PATENT SPECIFICATION (11) 1 570 988

1 570 988

(21) Application No. 48238/76 (22) Filed 19 Nov. 1976
(31) Convention Application No. 634 297
(32) Filed 21 Nov. 1975 in
(33) United States of America (US)
(44) Complete Specification published 9 July 1980
(51) INT CL³ C07D 487/04; A61K 31/40; (C07D 487/04, 205/00, 207/00)
(52) Index at acceptance
C2C 1173 1175 1176 1315 1341 1362 1410 1470 1510 200 202 214 215 220 221 225 226 22X 22Y 246 247 250 251 252 255 25Y 273 274 275 28X 290 292 29X 29Y 305 30Y 314 31Y 321 322 323 328 32Y 332 338 340 34Y 351 352 355 358 360 362 364 365 366 367 368 36Y 373 37Y 380 390 391 463 614 620 627 628 630 650 652 660 670 678 680 699 700 70Y 750 751 754 757 75X 76X 780 800 801 802 805 80Y AA QS RA RL RM RS SN

(72) Inventors BURTON GRANT CHRISTENSEN, RAYMOND ARMOND FIRESTONE and WILLIAM JOSEPH LEANZA

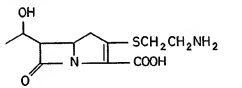
(54) ANTIBIOTICS OF THE THIENAMYCIN CLASS

(71) We, MERCK & CO INC., a corporation duly organized and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

There is a continuing need for new antibiotics, for, unfortunately, there is no static effectiveness of a given antibiotic because continued wide-scale usage of any antibiotic selectively gives rise to resistant strains of pathogens. In addition, the known antibiotics suffer from the disadvantage of being effective only against certain types of microorganisms. Accordingly, the search for new antibiotics continues.

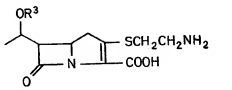
This invention relates to antibiotics of the thienamycin class.

Thienamycin, which has the formula:

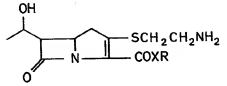


I

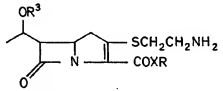
is disclosed and claimed in the specification of our copending application No. 48208/75 (1,498,087). It may serve as a starting material for making the compounds of the present invention, which are certain N-alkyl, N,N-dialkyl, and N,N,N-trialkyl derivatives of theinamycin and its stereoisomers, and their pharmaceutically acceptable salt, ester and amide derivatives. Compounds of the present invention are useful as antibiotics. Other convenient starting materials for making the N-alkylated thienamycins (and stereoisomers thereof) of the present invention are shown below (Ia, Ib, and Ic):



Ia



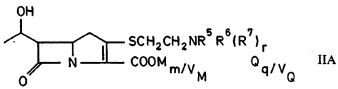
Ib



Ic

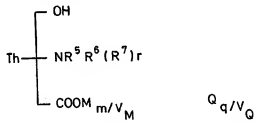
where R^3, X and R are as defined below. Starting materials Ia, Ib and Ic are also useful as antibiotics. Compounds Ia and Ic are disclosed and claimed in the specifications of our copending Patent Application Nos. 48237/76 (Serial No. 1570987) and 7667/77 (Serial No. 1569234), respectively.

Certain N-alkylated thienamycin compounds of the present invention are depicted by the following generic structural formula:



IIA

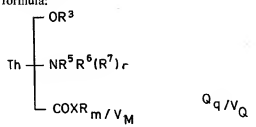
or, more conveniently, by the symbol:



IIA

in which "Th" symbolizes the bicyclic nucleus of theinamycin or its stereoisomeric derivative and the OH, amino, and carboxyl groups are illustrated.

The compounds of the present invention are more broadly defined as having the following formula:



II

In these formulae Q is an anion and M is H, an alkali or alkaline-earth metal cation or an amine cation. R^5, R^6 and (if present) R^7 are alike or different and each of them is independently a hydrogen atom (provided that not all of R^5, R^6 and R^7 are hydrogen at the same time), or a substituted or unsubstituted C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl radical or an unsubstituted or ring-substituted C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, (C_{3-8} cycloalkenyl) - C_{1-6} alkyl), (C_{3-8} cycloalkyl) - (C_{1-6} alkyl), C_{6-10} aryl, (C_{6-10} aryl) - (C_{1-6} alkyl) or (C_{6-10} aryl) - (C_{2-6} alkenyl)radical or an unsubstituted or ring-substituted monocyclic or bicyclic heteroaryl or heteroaralkyl comprising 4—10 ring atoms one or more of which is oxygen, nitrogen or sulphur, and 1—6 carbon atoms in the alkyl chain; and in which the substituent(s) is or are halogen, such as chlorine, bromine, iodine or fluorine, azido, cyano, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, a tri(C_{1-6} alkyl)ammonium salt, hydroxyl, C_{1-6} alkoxyl, C_{1-6} alkylthioalkyl, carboxyl, oxo (though oxo cannot be present on the nitrogen-attached carbon), (C_{1-6} alkoxy)-carbonyl, C_{2-10} acyloxy, carbamoyl, (C_{1-4} alkyl)-carbamoyl, di(C_{1-4} alkyl)-carbamoyl, cyanothio (—SCN) or nitro, or R_x and R_x are joined to form a polyethylene or oxygen-interrupted polymethylene residue;

V_Q and V_M are the valencies of Q and R (or M) respectively, V_M being 1 when R is other than M, and each of q, m and r is 0 or 1 and such that $m + r - q = 1$.

It will be recognized that the N,N,N - trisubstituted derivatives ($r = 1$ and R^7 is other than hydrogen) are quaternary ammonium compounds, the anion Q of which is not critical and may be, for example, a halide (such as chloride or bromide), phosphate or sulphate ($m=q=1$) or may be an internal salt ($m=q=0$). When $r=1$ and R^7 is hydrogen, the compounds are acid-addition salts.

X is oxygen, sulfur, NH or NR.

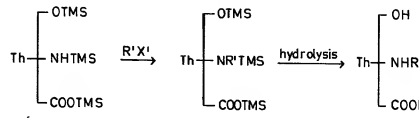
R is, *inter alia*, M as defined above (hydrogen or a salt), a conventional blocking group such as trialkylsilyl, acyl, or a pharmaceutically acceptable ester or imide residue. Such residues are known in the bicyclic β-lactam antibiotic art. The definition of R is given in greater detail below.

R^3 is hydrogen; acyl (generically the group OR^3 is classifiable as an ester); or a group such as alkyl, aryl, aralkyl, alkenyl or alkynyl; such that the group OR^3 is generically classifiable as an ether. The term "acyl" includes the alkanoyls and derivatives and analogues thereof such as thio analogues, in which the carbonyl oxygen is replaced by sulphur; and the sulphur and phosphorus acyl analogues such as substituted sulfonyl sulfenyl and sulfinyl radicals, and substituted P(III and V) radicals such as substituted phosphorous, phosphoric, phosphonous and phosphonic radicals respectively.

The particularly preferred compounds are those in which R^5, R^6, and (if present) R^7 are hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl, such as methyl, ethyl, propyl or allyl, benzyl, nuclear-substituted benzyl such as p-*t*-butyl benzyl, or a heteroaralkyl such as 4-pyridyl methyl, 2-furyl methyl or 2-thienyl methyl; and R^3, X and R are as defined above — especially when R^3 is hydrogen, X is oxygen and R is hydrogen.

The compounds of the present invention are prepared by reacting thienamycin, a suitable derivative or stereoisomer thereof or a suitably protected thienamycin species with an N-alkylating agent. The process of the present invention is not unduly critical and any of a variety of well known N-alkylation and analogous procedures may be used. The agent effecting the N-substitution is determined by the desired values of R^5, R^6 and R^7. The reaction may be conducted in any of a variety of solvent systems that are inert or substantially inert to the desired course of reaction. Suitable solvents include polar solvents such as water, C_{1-6} alkanols such as ethanol, dioxane, tetrahydrofuran (THF), acetonitrile, hexamethylphosphoramide (HMPA) are dimethylformamide (DMF) and mixtures (particularly aqueous mixtures) of the above; and non-polar solvents such as benzene and halohydrocarbons such as methylene chloride and chloroform. Typically the reaction is conducted at a temperature of from –40°C to 50°C for from 15 minutes to 5 hours. Usually, the reaction is conducted in the presence of an acid acceptor such as propylene oxide, magnesium oxide or potassium carbonate. The preferred N-substituting agents include active halides, sulfate esters, and Michael addition reagents. The following reagents are representative of such alkylating agents: methyl iodide, allyl bromide, bromo acetone, phenacyl bromide, benzyl bromide, ethylchloroacetate, propargyl bromide, 2-bromoethylethylether, dimethyl sulfate, methylfluorosulfonate, chloromethylthiocyanate, chloroethyl-methylsulfide, bromomethylcyclopropane, 2,4-dinitrofluorobenzene, 2-chloro-methylpyridine, acylonitrile, methyl methylacrylate and nitroethylene.

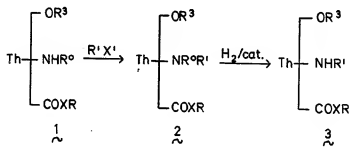
The N-monosubstituted compounds of the present invention may be prepared in any of a variety of ways. One convenient starting material is *tris*-trimethylsilyl thienamycin (Th(TMS)$_3$). When it is desired for R^a, R or R^3 and R to be other than hydrogen, the suitably derivatized starting materials such as Ia, Ib, and Ic (above), may be used. The reaction is carried out in any of the above-named non-protic solvents in the presence of the N-substituting agent chosen, usually a halide or sulfate. This step is followed by aqueous hydrolysis to produce the desired product. The following reaction diagram summarizes the process:



Th (TMS)$_3$

where TMS, R' is as defined above, R' is R^5, R^8 or R^7 and X' is a halogen or sulphate.

A second scheme for the preparation of monoalkyl compounds involves the N-substitution of an N-substituted thienamycin in which the substituent is an easily removable bulky group (R°) such as an aralkyl group, for example substituted and unsubstituted benzyl, benzylhydryl (—CH(C$_6$H$_5$)$_2$) or trityl (—C(C$_6$H$_5$)$_3$) where any ring substituent on the aralkyl is halogen, nitro, C$_{1-5}$ alkyl or C$_{1-5}$ alkoxy. The following reaction diagram summarizes this scheme:

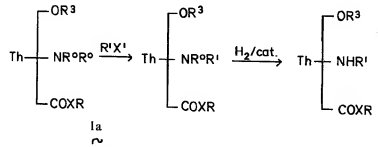


1 2 3

where all symbols are as defined above.

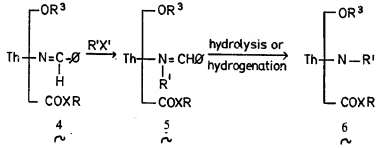
In words realtive to the above diagram, and using alkyl as the group to be substituted on the N atom, starting material 1, prepared for example by the reaction of thienamycin or derivative thereof with an aralkyl halide, is reacted with the N-alkylating agent R'X', as above-described, to provide the N-alkyl-N-aralkyl intermediate compound 2. The aralkyl N-substituent R° is readily removable to provide 3 by hydrogenolysis. Suitable conditions for this final cleavage step involve hydrogenating 2 in a solvent such as ethanol under hydrogen (1 to 4 atmospheres) in the presence of a catalyst such as platinum, palladium, or oxides thereof. The ultimate product of this reaction is primarily 3, the N-monoalkyl. However, there is some co-presence of N,N-dialkyl thienamycin. Such contaminating by-products may be separated by chromatographic methods and the magnitude of contamination may be minimized by using one equivalent or less of the alkylating agent R'X'.

A third method for the preparation of N-monoalkyl compounds, particularly N—(C$_{1-4}$ alkyl) compounds, is similar to the above described procedure except that the starting material 1a is N,N-diaralkyl thienamycin. The preparation of such starting materials is described below. The following reaction diagram summarized this process:



where all symbolism is as previously defined. It is to be noted that this scheme for the preparation of N-alkyl thienamycins is not complicated by the co-preparation of N,N-dialkyl thienamycins.

A fourth method which is particularly suitable for the preparation of N—(C_{1-8} alkyl) thienamycins involves the N-alkylation of a Schiff's Base of thienamycin. The following diagram summarizes the reaction.



in which ø is phenyl, R and R^3 are blocking groups, e.g. trimethylsilyl, X is preferably oxygen and all other symbols are as previously defined. The preferred Schiff's base is that obtained by reacting thienamycin with benzaldehyde or nuclear-substituted benzaldehyde. There is no criticality in the process for preparing such Schiff's bases. The reaction of 4 with the alkylating reagent R'X' provides intermediate compound 5 which upon aqueous hydrolysis or catalytic hydrogenolysis provides the desired N-alkyl thienamycin compound 6.

A fifth method for preparing N-alkyl thienamycins involves the desulfurization of an N-thioacyl thienamycin in the presence of a hydrogenation catalyst such as Raney Nickel:

where X is oxygen, R^3 and R are as previously defined but are preferably hydrogen, and R^8 is hydrogen, aryl, aralkyl or C_{1-8} alkyl. The N-thioacyl thienamycin starting materials are disclosed and claimed in the specification of our copending Application No. 48236/76 (Serial No. 1590986). The above desulfurization is typically conducted in polar protic solvents such as water, C_{1-8} alkanols such as ethanol, and aqueous mixtures thereof at a temperature of from 0.50°C for from 30 minutes to 5 hours.

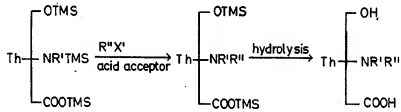
The N,N-dialkyl thienamycin derivatives of the present invention may be prepared in any of a variety of ways. The N-substituents may be the same ("symmetric") or different ("asymmetric"). The symmetric type may be prepared from starting material 1 when an excess of the alkylating agent is used. This process gives exclusively the N,N-disubstituted product. Hydrogenation of resulting

intermediate to cleave the N-aralkyl substituent provides the desired N,N-dialkyl thienamycin compound in the manner described above.

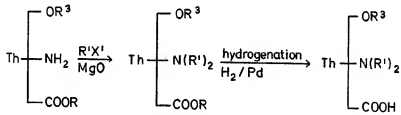
In general, the N,N-dialkyl thienamycin compounds may be prepared by directed alkylation when the alkylation reaction is conducted in water, a protic solvent or mixtures thereof without protection of the carboxyl group. However when direct alkylation is conducted in an aprotic solvent, such as HMPA, esterification of the free carboxyl group generally occurs. In cases where ester formation is not desired, the carboxyl group is preferably blocked by a conventional readily removable carboxyl blocking group. [Preparation of such carboxyl blocked thienamycin compounds is given below.] Further, it should be noted that direct N-alkylation of thienamycin usually provides a mixture of the mono-, di-, and trialkyl products the relative proportions of which are determined for steric reasons by the size of R′ of the alkylating reagent and the amount of reagent used. When R′ is small (less bulky), such as methyl and ethyl, the N,N,N-trialkyl compounds predominate. As the size of R′ increases, the mono- and dialkyl compounds predominate.

The symmetrical type may be prepared either by reductive alkylation with an aldehyde ($R''CHO$, where $-CH_2R'' = R^5$, R^6, or R^7), or by dialkylation of an ester of thienamycin by an alkyl halide or sulphate followed, if desired, by cleavage of the ester group by standard methods such as hydrogenation.

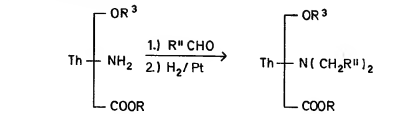
The asymmetric types may be prepared by reductive alkylation of a monoalkyl thienamycin compound with an appropriate aldehyde, or by alkylating the *tris*-trimethylsilyl - N - monoalkyl thienamycin with the alkylating agent of choice in the presence of an acid acceptor such as propylene oxide, K_2CO_3 or MgO. Again, any of the starting materials Ia, Ib, or Ic may be used to provide the corresponding O-, carboxyl, or O- and carboxyl derivative. The following diagram illustrate the above schemes:



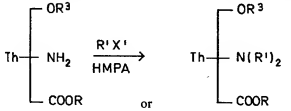
where all symbols are as defined above R′ may or may not be the same as R″, and R′ and R″ are radicals as defined for R^5, R^6 and R^7;

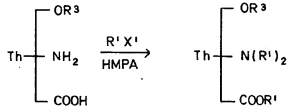


wherein R is as previously defined and is in the case of the final cleavage an easily removable blocking group such as benzyl or *p*-nitrobenzyl; R^3 is as defined above, are R′ = R^5, R^6 or R^7;



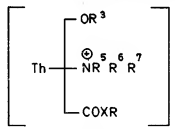
wherein $-CH_2R''$ = R^5, R^6 or R^7; and R and R^3 are as defined above.



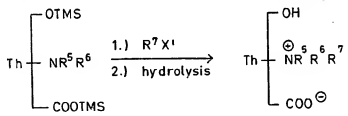


where R^3 is as defined; R' = R^5, R^6 or R^7; X' = halide or sulphate; and R is as defined, the special case of R = H being illustrated. Again it is to be noted that ester formation may be avoided, when operating upon the free acid, by conducting the alkylation in water or a protic solvent.

N,N,N-trialkyl thienamycin derivatives of the present invention may be prepared from thienamycin, an O-, carboxyl, or O- and carboxyl derivative thereof, or from the N,N-dialkyl compound by alkylation with an alkyl halide or sulphate. The carboxyl group may be protected by a conventional blocking group, such as benzyl or p-nitrobenzyl. It is to be noted, however, that R^3- and R-substituted N,N-dialkyl thienamycins are suitable substrates when it is desired to prepare compounds of the present invention having the following structure:



where the non-critical counter anion $A^{\ominus}$ has previously been identified. The following diagram is represented of the formation of an internal salt by this process:



where all substituents are as defined above.

In the representation of the compounds of the present invention (II, above), the radical represented by —COXR, is, *inter alia*, —COOH (X is oxygen and R is hydrogen) and all radicals known to be effective as pharmaceutically acceptable ester, anhydride (R is acyl) and amide radicals in the bicyclic β-lactam antibiotic art, such as the cephalosporins and penicillins and their nuclear analogues.

Suitable radicals (R) include conventional protecting or carboxyl blocking groups. The term "blocking group" is used in the same manner and in accordance with the teaching of U.S. Patent 3,697,515. Pharmaceutically acceptable thienamycin derivatives of the present invention falling in this class are given below. Suitable blocking esters thus include those selected from the following list which is representative and not intended to be an exhaustive list of possible ester groups, where X = 0 and R is given:

(i) R = $CR^a—R^b—R^c—$ where at least one of $R^a—$, $R^b—$ and $R^c—$ is an electron-donor, e.g. *p*-methoxyphenyl, 2,4,6-trimethylphenyl, 9-anthryl, methoxy, CH_2SCH_3, tetrahydrofur-2-yl, tetrahydropyran-2-yl or fur-2-yl. The remaining $R^a—$, $R^b—$ and $R^c—$ groups may be hydrogen or organic substituting groups. Suitable ester groups of this type include *p*-methoxybenzyloxycarbonyl and 2,4,6 - trimethylbenzyloxycarbonyl.

(ii) R is $CR^a—R^b—R^c—$ where at least one of $R^a—$, $R^b—$ and $R^c—$ is an electron-attracting group, e.g., benzol, *p*-nitrophenyl, 4-pyridyl, trichloromethyl, tribromomethyl, iodomethyl, cyanomethyl, ethoxycarbonylmethyl, arylsulphonyl-methyl, 2-dimethylsuylphoniummethyl salt, *o*-nitrophenyl or cyano. Suitable esters of this type include benzoylmethoxy-carbonyl, *p*-nitrobenzyloxycarbonyl, 4-pyridylmethoxycarbonyl, 2,2,2 - trichloroethoxycarbonyl and 2,2,2 - tribromo-ethoxycarbonyl.

(iii) R is $CR^a—R^b—R^c—$ where at least two of $R^a—$, $R^b—$ and $R^c—$ are hydrocarbon such as alkyl, e.g., methyl or ethyl, or aryl, e.g., phenyl and the remaining $R^a—$, $R^b—$ or $R^c—$, if there is one, is hydrogen. Suitable esters of this type include *t*-butyloxycarbonyl, *t*-amyloxycarbonyl, diphenylmethoxycarbonyl and tri-phenylmethoxycarbonyl.

(iv) R is adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl or tetrahydro-pyran-2-yl.

Silyl esters, under this category of blocking groups, may conveniently be prepared from a halosilane or a silazane of the formula:

R^4_3SiX'; $R^4_3Si.NHR^4$; $R^4_3Si.NH.COR^4$; $R^4_3Si.NH.CO.NH.SiR^4_3$; $R^4NH.CO.NH.SiR^4_3$; or $R^4COSiR^4_3$); $HN(SiR^4_3)_2$, where X' is a halogen such as chlorine or bromine and the various groups R^4, which can be the same or different, represent hydrogen, alkyl, e.g. methyl, ethyl, *n*-propyl, iso-propyl; aryl, e.g. phenyl; or aralkyl, e.g., benzyl.

More generally stated, pharmaceutically acceptable carboxyl derivatives of the present invention are those derived by reacting an N-acylated thienamycin (I above) with alcohols, phenols, mercaptans, thiophenols, or acylating reagents that yield compounds 2 above, which are then derivatized to establish the R^3 group of the compounds of the present invention (II, above).

For example, esters and amides of interest are the compounds of the formula II above having the following group at the 2-position: —COXR where X is oxygen, sulfur, NH or NR, and R (or each R) is alkyl having 1—10 carbon atoms, straight or branched, such as methyl, ethyl, *t*-butyl, pentyl and decyl; carbonylmethyl including phenacyl nuclear-substituted phenacyl in which the substituent is chloro, bromo, fluoro or C_{1-5} alkyl (e.g. *p*-bromophenacyl or *p*-*t*-butylphenacyl), acetoxy-acetylmethyl, pivaloxyacetylmethyl, carboxymethyl and its alkyl and aryl esters; α - carboxy - α - isopropyl; aminoalkyl including 2-methylaminoethyl, 2-diethylaminoethyl, 2-acetamidoethyl, phthalimidomethyl and succinimidomethyl: (C_{1-10} alkoxy) - (C_{1-5} alkyl) in which the alkoxy residue can be branched, straight or cyclic, such as methoxymethyl, ethoxymethyl, isopropoxymethyl, decyloxymethyl, ethoxypropyl, decyloxypentyl or cyclohexyloxymethyl; (C_{1-5} alkanoyloxy) - (C_{1-5} alkyl) in which the alkanoyloxy portion is straight or branched, such as acetoxy-methyl, pivaloyloxymethyl, acetoxyethyl, propionyloxyethyl, or acetoxypropyl; halogenated straight or branched C_{1-5} alkyl in which the halogen is iodine, chlorine, bromine and/or fluorine, e.g. 2,2,2 - trichloroethyl, trifluoroethyl, 2-bromopropyl, diiodomethyl, 2-chloroethyl, or 2-bromoethyl, and also including C_{1-5} perhaloalkyl; alkenyl having 2—10 carbon atoms, either straight or branched, e.g., allyl, 2-propenyl, 3-butenyl, 4-butenyl, 4-pentenyl, 2-butenyl, 3-pentenyl, 3-methyl - 3 - butenyl, methallyl and 1,4 - cyclohexadien - 1 - yl - methyl; alkynyl having 2—10 carbon atoms, either straight or branched, e.g., 3 - pentynyl, propargyl, ethynyl and 3-butyn-1-yl; alkanoyl, either straight or branched, having 1—10 carbon atoms, such as pivaloyl, acetyl and propionyl; C_{3-14} alkoxycarbonyl-alkyl; C_{4-21} dialkylaminoacetoxyalkyl; C_{2-13} alkanamidoalkyl; aralkyl in which the alkyl residue has 1—3 carbon atoms and the aryl residue 6—10 carbon atoms, such as benzyl, benzhydryl, substituted benzyl or benzhydryl, e.g., benzyl or benzhydryl

substituted with 1—3 substituents such as benzyl, phenoxy, halo, C_{1-4} alkyl, alkanoyloxy of 1—5 carbon atoms, C_{1-4} alkoxy, hydroxy, nitro, blocked carboxy, or combinations thereof, e.g., *p*-chlorobenzyl, *o*-nitrobenzyl, 3,5-dinitrobenzyl, *p*-methoxybenzyl, *m*-benzoylbenzyl, *p-t*-butylbenzyl, *m*-phenoxybenzyl, *p*-benzoylbenzyl, *p*-nitrobenzyl, 3,5-dichloro - 4 - hydroxybenzyl, *p*-methoxycarbonylbenzyl, *p*-methoxybenzhydryl, *p*-carboxybenzyl (the latter being either the free acid, ester or the sodium salt), 2,4,6-trimethylbenzyl, *p*-pivaloyloxybenzyl, *p-t*-butoxycarbonyl benzyl, *p*-methylbenzyl, *p*-benzoyloxybenzyl, *p*-acetoxybenzyl, *p* - 2 - ethylhexanoylbenzyl, *p*-ethoxycarbonylbenzyl, *p*-benzoylthionenzyl, *p*-benzamidobenzyl, *o*-pivaloyloxybenzyl, *m*-pivaloyloxybenzyl, *p*-isopropoxybenzyl or *p-t*-butoxybenzyl, as well as cyclic analogues thereof; monocyclic and bicyclic heteroaralkyl or heterocyclylalkyl in which there are 4 to 10 atoms in the ring, the hetero atom or atoms being oxygen, sulfur and/or nitrogen, and 1 to 6 carbon atoms in the alkyl chain, e.g. 2,2 - dimethyl - 5 - coumaranmethyl, 5-indanylmethyl, *p*-trimethylsilylbenzyl, 3,5 - bis - *t* - butoxy - 4 - hydroxybenzyl, 2-thienylmethyl, 2-furylmethyl, 3 - *t* - butyl - 5 - isothiazolmethyl, 6 - pivaloyloxy - 3 - pyridazinylethyl or 5 - phenylthio - 1 - tetrazolylmethyl; phthalidyl; phenylethyl, 2 - (*p* - methylphenyl)ethyl, and their arylthioalkyl analogues; aryloxy(C_{1-5} alkyl) where aryl is preferably a phenyl ring having 0—3 substituents, preferably 0 or 1 substituent in the ortho or para positions, e.g., (4-methoxy)phenoxymethyl, phenoxymethyl, (4-chloro)phenoxymethyl, (4-nitro)phenoxymethyl, (4-benzyloxy)-phenoxymethyl, (4-methyl)phenoxymethyl, (2-methoxy)phenoxymethyl, (1-phenoxy)ethyl, (4-amino)phenoxymethyl, (4-methoxy)phenylthiomethyl, (4-chloro)phenylthiomethyl or phenylthioethyl; aryl and nuclear-substituted aryl having 6 to 10 ring carbon atoms and in which the substituents is/are hydroxy, C_{1-5} alkyl, chloro, bromo or fluoro, e.g. phenyl, 5-indanyl or substituted phenyl having 1—3 substituents, preferably one substituent in the ortho or para position, such as (4-methyl)phenyl, (4-hydoxy)phenyl, (4-*t*-butyl)phenyl, *p*-nitrophenyl, 3,5-dinitrophenyl or *p*-carboxyphenyl, the latter having either the free acid or the sodium salt form; phenyl-(C_{2-5} alkenyl), such as 3-phenyl - 2 - propenyl; benzyloxy-(C_{1-5} alkyl) such as benzyloxymethyl, (4-nitro)benzyloxymethyl or (4-chloro)benzyloxymethyl; alkylthioalkyl where the alkylthio residue has 1—10 and preferably 1—6 carbon atoms, and can be branched or straight, and the alkyl portion has 1—6 carbon atoms, such as methylthioethyl, ethylthioethyl, decylthiobutyl, methylthiopropyl, isopropylthioethyl or methylthiobutyl; cycloalkylthioalkyl containing 4 to 12 carbon atoms, e.g.cyclohexylthiomethyl, or (C_{2-10} acylthio) - (C_{1-5} alkyl).

In addition to the esters and the thio esters listed above, amides are also embraced by the present invention, i.e., compounds where X is the

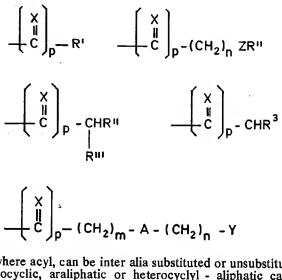
group. Representative of such amides, Th—CONR′R, are those in which R′ is hydrogen, methyl, ethyl phenyl, *p*-methoxyphenyl, benzyl, carboxymethyl, methylthioethyl, or heteroaryl; also embraced by —COXR are anhydrides in which R is, for example, benzyloxycarbonyl, ethoxycarbonyl, benzoyl, and pivaloyl.

The preferred —COXR radicals of the present invention are those in which, in Formula II above, X is oxygen, sulphur, inino (—NH—) or C_{1-5} alkylimino, and R is C_{1-5} alkyl, C_{2-5} alkenyl, such as methallyl, 3-methylbutenyl or 3-butenyl; methylthioethyl; benzyl; substituted benzyl, such as *p-t*-butylbenzyl, *m*-phenoxybenzyl, *p*-pivaloyloxybenzyl or *p*-nitrobenzyl; pivaloyloxymethyl, 3-phthalidyl, acetoxymethyl, propionyloxymethyl, acetylthiomethyl, pivaloylthiomethyl, allyl, 4-butenyl, 2-butenyl, 3 - methyl - 2 - butenyl, phenacyl, acetoxyacetylmethyl, methoxymethyl, *p*-acetoxybenzyl, *p*-pivaloyloxybenzyl, *p*-isopropoxybenzyl, 5-indanylmethyl, 5-indanyl, benzyloxymethyl, ethylthioethyl, methylthiopropyl, methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, dimethylaminoacetoxymethyl, crotonolacton - 3 - yl, or acetamidomethyl.

In Formula II and IIA above, the radical R^3 is, in addition to hydrogen, (1) acyl (gererically the group —OR^3 is classifiable as an ester); or (2) R^3 is a radical (e.g. alkyl, aryl or aralkyl) such that the group —OR^3 is classifiable as an ether. For the esters, R^3 is selected from the following definition of acyl radicals (p = 1). In the ethers, R^3 is selected from the same acyl radicals in which the carbonyl residue,

or more generally

is deleted ($p = 0$). Thus R^3 is selected from the following radicals, where all symbolism is defined below:



Thus, R^3, where acyl, can be inter alia substituted or unsubstituted aliphatic, aromatic, heterocyclic, araliphatic or heterocyclyl - aliphatic carboxylic acid radical, a substituted or unsubstituted carbamoyl radical or a carbothioic acid radical. One group of acyl radicals can be represented by the general formula:

where X is 0 or S and R'' represents hydrogen; amino; substituted amino such as C_{1-6} alkylamino of di(C_{1-6} alkyl)amino in which the alkyl radical(s) are substituted or unsubstituted; straight or branched-chain alkyl, especially C_{1-6} alkyl; mercapto, substituted mercapto such as alkylthio, typically comprising 1 to 6 carbon atoms, or arylthio, typically comprising 6 to 10 carbon atoms; hydroxy; substituted hydroxy such as alkoxy, typically comprising 1 to 6 carbon atoms, or aryloxy, typically comprising 6 to 10 carbon atoms; arkenyl or alkynyl, typically comprising 2 to 6 carbon atoms; aryl, such as phenyl; aralkyl, such as benzyl; cycloalkyl, typically comprising 3 to 6 carbon atoms; or a heteroaryl or heteroaralkyl group (mono- and bicyclic) in which the alkyl residue (if any) typically comprises 1 to 3 carbon atoms and the heterocyclic ring typically comprises 4—10 atoms and the hetero atom or atoms is/are pre-preferably O,N and/or S provided that R'' is not mercapto or hydroxy unless Z or R''' is present, that R'' is not mercapto or hydroxy if Z is oxygen, that R'' is not amino or hydroxy if Z is sulfur, and that R'' is not mercapto if Z is imino; such above-listed groups can be unsubstituted or can be substituted by radicals such as OH, SH, SR^g (R^g is C_{1-6} alkyl or aryl such as phenyl), alkyl or alkoxy groups having 1 to 6 carbon atoms, halogens, viz. Cl, Br, F or I, cyano, carboxy, sulfamino, carbamoyl, sulfonyl, azido, amino, substituted amino, such as (C_{1-6} alkyl)-substituted amino including quaternary ammonium, C_{1-6} halogenated alkyl such as trifluoromethyl, carboxy(C_{1-6} alkyl), carbamoyl(C_{1-6} alkyl), N-substituted carbamoyl(C_{1-6} alkyl), amidino, guanidino, N-substituted guanidino or guanidino-(C_{1-6} alkyl). Representative exaamples of such acyl groups that might be mentioned are those in which R'' is benzyl, *p*-hydroxybenzyl, 4 - amino - 4 - carboxybutyl, methyl, (in which case, when X is O, the acyl radical is acetyl),

cyanomethyl, 2 - pentenyl, *n* - amyl, *n* - heptyl, ethyl, 3- or 4 - nitrobenzyl, phenethyl, *β,β* - diphenylethyl, methyldiphenylmethyl, triphenylmethyl, 2 - methoxyphenyl, 2,6 - dimethoxyphenyl, 2,4,6 - trimethoxyphenyl, 3,5 - dimethyl - 4 - isoxazolyl, 3 - butyl - 5 - methyl - 4 - isoxazolyl, 5 - methyl - 3 - phenyl - 4 - isoxazolyl, 3 - (2 - chlorophenyl) - 5 - methyl - 4 - isoxazolyl, 3 - (2,6 - dichlorophenyl) - 5 - methyl - 4 - isoxazolyl, *D* - 4 - amino - 4 - carboxybutyl, *D* - 4 - N - benzoylamino - 4 - carboxy - *n* - butyl, *p* - aminobenzyl, *o* - aminobenzyl, *m* - aminobenzyl, *p* - dimethylaminobenzyl, (3 - pyridyl)methyl, 2 - ethoxy - 1 - naphthyl, 3 - carboxy - 2 - quinoxalinyl, - 3 - (2,6 - dichlorophenyl) - 5 - (2 - furyl) - 4 - isoxazolyl, 3 - phenyl - 4 - isoxazolyl, 5 - methyl - 3 - (4 - guanidinophenyl) - 4 - isoxazolyl, 4 - guanidinomethylphenyl, 4 - guanidinomethylbenzyl, 4 - guanidinobenzyl, 4 - guanidinophenyl, 2,6 - dimethoxy - 4 - guanidinophenyl, *o* - sulfobenzyl, *p* - carboxymethylbenzyl, *p* - carbamoylmethylbenzyl, *m* - fluorobenzyl, *m* - bromobenzyl, *p* - chlorobenzyl, *p* - methoxybenzyl, 1 - naphthylmethyl, 3 - isothiazolylmethyl, 4 - isothiazolylmethyl, 5 - isothiazolylmethyl, guanylthiomethyl, 4 - pyridylmethyl, 5 - isoxazolylmethyl, 4 - methoxy - 5 - isoxazolylmethyl, 4 - methyl - 5 - isoxazolylmethyl, 1 - imidazolylmethyl, 2 - benzofuranylmethyl, 2 - indolylmethyl, 2 - phenylvinyl, 2 - phenylethynyl, 1 - aminocyclohexyl, 2 - and 3 - thienylaminomethyl, 2 - (5 - nitrofuranyl)vinyl, phenyl, *o* - methoxyphenyl, *o* - chlorophenyl, *o* - phenylphenyl, *p* - aminomethylbenzyl, 1 - (5 - cyanotriazolyl)methyl, difluoromethyl, dichloromethyl, dibromomethyl, 1 - (3 - methylimidazolyl)methyl, (2 or 3) - (5 - carboxymethylthienyl)methyl, (2 or 3) - (4 - carbomoylthienyl)methyl, (2 or 3) - (5 - methylthienyl)methyl, (2 or 3) - (5 - methoxythienyl) - methyl, (2 or 3) - (4 - chlorothienyl) - methyl, (2 or 3) - (5 - sulfothienyl)methyl, (2 or 3) - (5 - carboxythienyl)methyl, 3 - (1,2,5 - thiadiazolyl)methyl, 3 - (4 - methoxy - 1,2,5 - thiadiazolyl)methyl, 2 - furylmethyl, 2 - (5 - nitrofuryl)methyl, 3 - furylmethyl, 2 - thienylmethyl, 3 - thienylmethyl, tetrazolylmethyl, benzamidinomethyl and cyclohexylamidinomethyl.

The acyl group can also be a radical of the formula:

or

where X is 0 or S and *n* is 0, 1, 2, 3 or 4, Z represents oxygen, sulfur, carbonyl or nitrogen, R'' is defined as above and R* is as defined below. Representative members of the substituent

that might be mentioned are allylthiomethyl, phenylthiomethyl, butylthiomethyl, *α* - chlorocrotylthiomethyl, phenoxymethyl, phenoxyethyl, phenoxybutyl, phenoxybenzyl, phenoxyphenoxymethyl, (dimethylmethoxy)methyl, (dimethylbutoxy)methyl, (dimethylphenoxy)methyl, 4 - guanidinophenoxymethyl, 4 - pyridylthiomethyl, *p* - (carboxymethyl)phenoxymethyl, *p* - (carboxymethyl)-phenylthiomethyl, 2 - thiazolylthiomethyl, *p* - (sulfo)phenoxymethyl, 2 - pyrimidinylthiomethyl, phenethylthiomethyl, 1 - (5,6,7,8 - tetrahydronaphthyl)-oxymethyl, N - methyl - 4 - pyridylthio, benzyloxy, methoxy, ethoxy, phenoxy, phenylthio, amino, methylamino, dimethylamino, a pyridinium methyl or trimethylammonium - methyl non-toxic salt, cyanomethylthiomethyl or trifluoromethylthiomethyl. R* is 4 - pyridylethyl, 4 - pyridylpropyl, 4 - pyridylbutyl, 3 - imidazolylethyl, 3 - imidazolylpropyl, 3 - imidazolylbutyl, 1 - pyrrolylethyl, 1 - pyrrolylpropyl and 1 - pyrrolylbutyl.

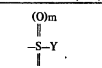
Alternatively, the acyl group can be a radical of the formula:

where R'' is defined as above and R''' is azido, carbamoyl, guanidino, amidino, acyloxy, halo, namely Cl, F, Br I, sulfamino, tetrazolyl, sulfo, carboxy, carbalkoxy, phosphono, alkoxy or arylthio. Representative members of the substituent

that might be mentioned are α - aminobenzyl, α - amino - (2 - thienyl)methyl, α - (methylamino)benzyl, α - amino - methylthiopropyl, α - amino - (3 or 4 - chloro - benzyl, α - amino - (3 or 4) - hydroxybenzyl, α - amino- 2,4 - dichlorobenzyl, α - amino - 3,4 - dichlorobenzyl, *D*(-) - α - hydroxybenzyl, α - carboxybenzyl, α - amino - (3 - thienyl)methyl, *D* - (-) - α - amino - 3 - chloro - 4 - hydroxybenzyl, α - amino(cyclohexyl)methyl, α - (5 - tetrazolyl)benzyl, 2 - thienyl - carboxymethyl, 3 - thienyl - carboxymethyl, 2 - furyl - carboxymethyl, 3 - furyl - carboxymethyl, α - sulfaminobenzyl, 3 - thienyl - sulfaminomethyl, α - (N - methylsulfamino)benzyl, *D*(-) - 2 - thienyl - guanidinomethyl, *D*(-) - α - guanidinobenzyl, α - guanylureidobenzyl, α - hydroxybenzyl, α - azidobenzyl, α - fluorobenzyl, 4 - (5 - methoxy - 1,3 - oxadiazolyl) - aminomethyl, 4 - (5 - methoxy - 1,3 - oxadiazolyl) - hydroxymethyl, 4 - (5 - methoxy - 1,3 - sulfadiazolyl) - hydroxymethyl, 4 - (5 - chlorothienyl) - aminomethyl, 2 - (5 - chlorothienyl) - hydroxy - methyl, 2 - (5 - chlorothienyl) - carboxy - methyl, 3 - (1,2 - thiazolyl) - aminomethyl, 3- (1,2 - thiazolyl) - hydroxymethyl, 3 - (1,2 - thiazolyl) - carboxymethyl, 2 - (1,4 - thiazolyl) - aminomethyl, 2 - (1,4 - thiazolyl) - hydroxymethyl, 2 - (1,4 - thiazolyl) - carboxymethyl, 2 - benzothienylaminomethyl, 2 - benzothienylhydroxymethyl, 2 - benzothienylcarboxymethyl, α - sulphobenzyl or α - phosphonobenzyl. The acyl radical can also be α - diethylphosphono or α - monoethylphosphono. Further acyl radicals of interest when X = oxygen are:

where R^3' and R^4' are as defined below. R^3' represents hydrogen, chloro, fluoro, bromo, iodo, amino, guanidino, phosphono, hydroxy, tetrazolyl, carboxy, sulfo or sulfamino and R^4' represents phenyl, substituted phenyl, a mono- or bicyclic heterocyclyl containing one or more oxygen, sulfur or nitrogen atoms in the ring, (such as furyl, quinoxalyl, thienyl, quinolyl, quinazolyl, thiazolyl, isothiazolyl, tetrazolyl, oxadiazolyl or thiadiazolyl), phenylthio, phenyloxy, alkyl of 1—6 carbon atoms, heterocyclic-thio or substituted heterocyclic-thio groups; or cyano. The substituents on the residues R^3' and R^4' can be halo, carboxymethyl, guanidino. guanidinomethyl, carboxamidomethyl, aminomethyl, nitro, methoxy or methyl. When R^3' is hydrogen, hydroxy, amino or carboxy and R^4' is phenyl or a (5 or 6) - membered heterocyclic ring having one or two sulfur, oxygen or nitrogen hetero atom such as tetrazolyl, thienyl, furyl and phenyl, the following acyl radicals are representative: phenylacetyl, 3 - bromophenylacetyl, *p* - aminomethylphenylacetyl, 4 - carboxymethylphenylacetyl, 4 - carboxyamidomethylphenylacetyl, 2 - furylacetyl, 5 - nitro - 2 - furylacetyl, 3 - furylacetyl, 2 - thienylacetyl, 5 - chloro - 2 - thienyl - acetyl, 5 - methoxy - 2 - thienyl - acetyl, α - guanidino - 2 - thienylacetyl, 3 - thienyl - acetyl, 2 - (4 - methylthienyl)acetyl, 3 - isothiazolylacetyl, 4 - methoxy - 3 - isothiazolylacetyl, 4 - isothiazolylacetyl, 3 - methyl - 4 - isothiazolylacetyl, 5 - isothiazolylacetyl, 3 - chloro - 5 - isothiazolylacetyl, 3 - methyl - 1,2,5 - oxadiazolylacetyl, 1,2,5 - thiadiazolyl - 4 - acetyl, 3 - methyl - 1,2,5 - thiadiazolylacetyl, 3 - chloro - 1,2,5 - thiadiazolyl - acetyl, 3 - methoxy - 1,2,5 - thiadiazolylacetyl, phenylthioacetyl, 4 - pyridylthioacetyl, cyanoacetyl, 1-tetrazolylacetyl, α - fluorophenylacetyl, *D* - phenylglycyl, 4 - hydroxy - *D* - phenyl - glycyl, 2 - thienylglycyl, 3 - thienylglycyl, phenylmalonyl, 3 - chlorophenylmalonyl, 2 - thienylmalonyl, 3 - thienylmalonyl, α - phosphonophenylacetyl, α - amino cyclohexadienylacetyl, α - sulfaminophenylacetyl, α - hydroxyphenylacetyl, α - tetrazolylphenylacetyl and α - sulfophenylacetyl.

The acyl radical R^3 may also be a sulphur (1) or phosphorus (2) radical:



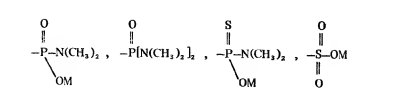
(1) (2)

in which, with respect to (1) each of m and n is 0 or 1 and Y is $O^{\ominus}M^{\oplus}$, $—N(R'')_2$, and R''; where $M^{\oplus}$ is hydrogen, an alkali metal cation, an alkaline-earth metal cation or an organic base; and R'' is as defined above, e.g., alkyl, alkenyl, aryl and heteroaryl. With respect to (2) X = 0 or S; n = 0 or 1; and each of Y' and Y'', independently of the other, is $O^{\ominus}M^{\oplus}$, $—N(R'')_2$, —R'' or —ZR'' where all symbols are as defined above, e.g., R'' and ZR'' may be alkyl, alkenyl, aryl or heteroaryloxy; or Y' and Y'', including R'' residues, are joined together to form cyclic ester, ester-amide and amide functions.

A preferred group of values of R^3 is the following:— sulfo, phosphono, carbamoyl, methylsulfonyl, sulfamoyl, dimethylsulfamoyl, N - methylcarbamoyl, bromoacetyl, hydroxyacetyl, aminoacetyl, dimethylaminoacetyl, trimethylammoniumacetyl, amidinoacetyl, guanidinoacetyl, methoxyacetyl, guanylacetyl, guanylthioacetyl, phosphamoyl, phosphonothioyl, thiocarbamoyl, methoxymethyl, hydroxyethyl, methoxyethyl, dimethylaminomethyl, dimethylaminoethyl, methylthiomethyl, amidinomethyl and guanidimethyl.

Other values of R^3 of particular interest are conventionally known N-blocking groups such as carbobenzyloxy, ring-substituted carbobenzyloxy such as *o* and *p* - nitrocarbobenzyloxy, *p* - methoxycarbobenzyloxy, chloroacetyl, bromoacetyl, phenylacetyl, *t* - butoxycarbonyl, trifluoroacetyl, bromoethoxycarbonyl, 9 - fluorenylmethoxycarbonyl, dichloroacetyl, *o* - nitrophenylsulfenyl, 2,2,2 - trichloroethoxycarbonyl, bromo - *t* - butoxycarbonyl, phenoxyacetyl, and tri(C_{1-6} alkyl)silyl, e.g. trimethylsilyl and *t* - butyldimethylsilyl.

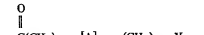
The following radicals, according to the foregoing definition of acyl, are preferred: formyl, propionyl, butyryl, chloroacetyl, methoxyacetyl, aminoacetyl, methoxycarbonyl, ethoxycarbonyl, methylcarbamoyl, ethylcarbamoyl, phenylthiocarbonyl, 3 - amino-propionyl, 4 - aminobutyryl, N - methylaminoacetyl, N,N - dimethylaminoacetyl, an N,N,N - trimethylammoniumacetyl salt, 3 - (N,N - dimethyl)aminopropionyl, a 3 - (N,N,N - trimethyl) - ammonium propionyl salt, an N,N,N - triethylammoniumacetyl salt, a pyridiniumacetyl salt, guanylthioacetyl, guanidinoacetyl, 3 - guanidinopropionyl, N^3 - methylguanidinopropionyl, hydroxyacetyl, 3 - hydroxypropionyl, acryloyl, propynoyl, malonyl, phenoxycarbonyl, amidinoacetyl, acetamidinoacetyl, amidinopropionyl, acetamidinopropionyl, guanylureidoacetyl, guanylcarbamoyl, carboxymethylaminoacetyl, phosphonoacetylaminoacetyl, N^2 - dimethylaminoacetamidinopropionyl, ureidocarbonyl, dimethylaminoguanylthioacetyl, a 3 - (1 - methyl - 4 - pyridinium) - propionyl salt, 3 - (5 - aminoimidazol - 1 - yl)propionyl, 3 - methyl - 1 - imidazoliumacetyl salt, 3 - sydnonylacetyl, *o* - amino - methylbenzoyl, *o* - aminobenzoyl,



or 

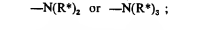
where M is as defined above, and is in particular sodium.

Especially preferred acyl radicals are terminally substituted acyls in which the substituent is one of certain basic groups. Such preferred substituted acyls may be represented by the following formula:

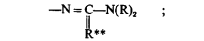


and these radicals and the corresponding radicals in which the

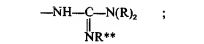
group is omitted are also preferred values of R^3. In the formula q is 0 or 1; each of m and n, independently of the other, is 0, 1, 2, 3, 4 or 5; A is O, —NR°— (where R° is hydrogen or C_{1-6} alkyl) or S, and Y is an amino or substituted amino radical of formula:



an amidino or substituted amidino radical of formula:



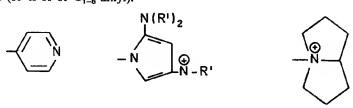
a guanidino or substituted guanidino radical of formula:

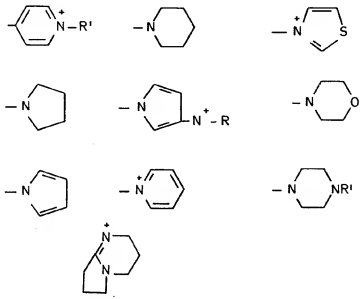


or a guanyl or substituted guanyl radical of formula:

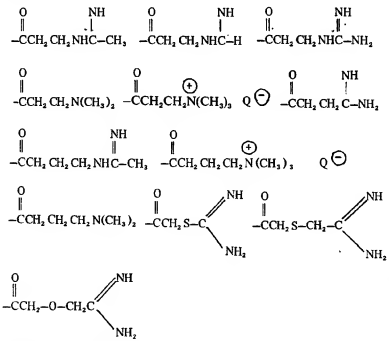
where each R, independently of the other, is hydrogen; $N(R^\circ)_2$ (where R° is hydrogen or C_{1-6} alkyl); C_{1-6} alkyl, C_{1-6} alkoxyl; (C_{1-6} alkoxy) - (C_{2-6} alkyl), C_{3-6} cycloalkyl or cycloalkyl - (C_{1-3} alkyl) or the two R groups are joined to form, together with the N atom to which they are attached, a ring having 3 to 6 atoms; R* is a radical as defined for R except that if cycloalkylalkyl, it must be (C_{3-6} cycloalkyl) - C_{1-3} alkyl; and R** is a radical as defined for R or a (C_{1-6} alkoxy) - methyl radical; or Y is a monocylic or bicyclic heterocyclic aromatic or non-aromatic radical having 4 to 10 nuclear atoms and in which the hetero atom or atoms are nitrogen and optionally oxygen or sulfur.

Such heterocycles are representatively illustrated by the following list of radicals (R' is H or C_{1-6} alkyl):





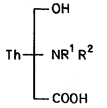
The following specific acyl radicals falling within this class are additionally representative and are preferred:



However, it is to be understood that any acyl radical may be used in the practice of the invention and is to be considered within the scope of the invention.

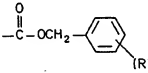
Preparation of Starting Materials Ia, Ib, and Ic

The above-described starting materials are conveniently prepared from an N-protected thienamycin (1), such as an N-acylated thienamycin (1).



(I)

where R^1 and R^2 are hydrogen or an above-defined radical. Preferably R^1 is hydrogen and R^2 is an easily removable blocking group such as: benzyloxycarbonyl, ring-substituted benzyloxycarbonyl such as *o*- and *p* - nitrobenzyloxycarbonyl, *p* - methoxybenzyloxycarbonyl, chloroacetyl, bromoacetyl, phenylacetyl, *t* - butyoxycarbonyl, trifluoracetyl, bromoethoxycarbonyl, 9 - fluorenylmethoxycarbonyl, dichloroacetyl, 2,2,2 - trichloroethoxycarbonyl, bromo - *t* - butoxycarbonyl, phenoxyacetyl; non-acyl protective groups such as *o* - nitrophenylsulfenyl, and tri(C_{1-6} alkyl)silyl, for example, trimethylsilyl and *t* - butyldimethylsilyl, are also of interest. The especially preferred N-blocking groups are the radicals of formula:



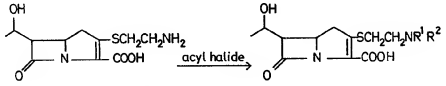
where *n* is 0, 1 or 2 and R' is C_{1-6} alkoxy or nitro; and bromo - *t* - butoxycarbonyl.

The ultimate N-deblocking procedure for the preparation of Ia, Ib or Ic is accomplished by any of a variety of well known procedures, which include hydrolysis or hydrogenation; suitable hydrogenation conditions involve a solvent such as a C_{1-6} alkanol in the presence of a hydrogenation catalyst such as palladium, platinum or an oxide thereof.

The N-acylated intermediate compound (I, above) is prepared by treating thienamycin or an enantiomer of thienamycin (I) with an acylating agent, for example, an acyl halide or acyl anhydride such as an aliphatic, aromatic, heterocyclic, araliphatic or heterocyclic aliphatic carboxylic acid halide or anhydride. Other acylating agents may also be used for example, mixed carboxylic acid anhydrides and particularly C_{1-6} alkyl esters of mixed carboxylic-carbonic anhydrides, i.e. compounds of formula R'—CO—O—CO—OR''; also carboxylic acids in the presence of a carbodiimide, such as 1,3 - dicyclohexylcarbodiimide, and activated esters of a carboxylic acid such as the *p* - nitrophenyl ester.

Such N-acylated thienamycin starting materials are described and claimed in the specification of our copending Application No. 48236/76 (Serial No. 1570986).

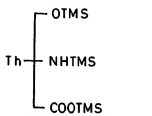
The acylation reaction may be conducted at a temperature in the range –200 to 100°C., but is preferably conducted at a temperature in the range –9°C. to 25°C. Any solvent in which the reactants are soluble and substantially inert may be used, for example, polar solvents such as water, alcohols and polar organic solvents in general such as dimethylformamide (DMF), hexamethyl, phosphoramide (HMPA), acetone, dioxane tetrahydrofuran (THF), acetonitrile, heterocyclic amines such as pyridine, ethyl acetate, aqueous mixtures of the above, as well as halogenated solvents such as methylene chloride and chloroform. The reaction is conducted for a period of time of from five minutes to a maximum of three hours, but in general, a reaction time of 0.5 to one hour is sufficient. The following equation illustrates this process using a carboxylic acid halide; however, it is to be understood that by substituting a carboxylic acid anhydride or other functionally equivalent acylating agent similar products may be obtained.



I 1

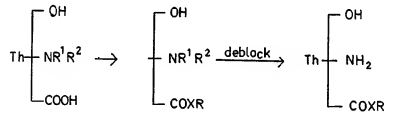
Generally when the above-described acylating reaction uses an acid halide (suitable halides are chlorides iodides and bromides) or anhydride the reaction is conducted in water or an aqueous mixture of a polar organic solvent such as acetone, dioxane, THF, DMF or acetonitrile in the presence of a suitable acceptor base such as $NaHCO_3$, MgO, NaOH or K_2HOP_4.

In carrying out the reactions described herein, it is generally not necessary to protect the 2-carboxy group or the 1'-hydroxy group; however, in cases where the acylating reagent is exceedingly water-sensitive it is sometimes advantageous to perform the acylation in a non-aqueous solvent system. Triorganosilyl (or tin) derivatives of thienamycin (or its enantioners) are suitable. Silylation proceeds rapidly to give the *tris*-triorganosilyl derivative, for example *tris*-trimethylsilyl thienamycin $Th(TMS)_3$:



Such derivatives, which are readily soluble in organic solvents, are conveniently prepared by treating thienamycin with an excess of hexamethyldisilazane and a stoichiometric amount of trimethylchlorosilane at 25°C., with vigorous stirring under a N_2 atmosphere. The resulting NH_4Cl is removed by centrifugation and the solvent is removed by evaporation to provide the desired silyl derivative.

The intermediate starting materials Ib are prepared according to the following scheme; however, it should be noted that direct esterification, without protection of the amino group, is also possible.



I Ib Ib

wherein all symbolism is as previously defined.

In general, the transformation (I→Ib) is accomplished by known procedures, including:

1.) Reaction of I (or I) with a diazoalkane such as diazomethane, phenyldiazomethane or diphenyldiazomethane, in a solvent such as dioxane, ethylacetate or acetonitrile at a temperature of from 0°C to reflux for from a few minutes to 2 hours.

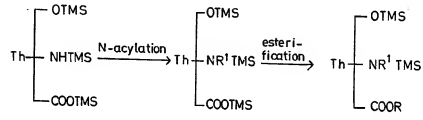
2.) Reaction of an alkali metal salt of I with an activated alkyl halide such as methyliodide, benzyl bromide, or *m* - phenoxybenzyl bromide, *p* - *t* - butylbenzyl bromide or pivaloyloxymethyl chloride. Suitable reaction conditions include

solvents such as hexamethylphosphoramide at a temperature of from 0°C. to 60°C. for from a few minutes to 4 hours.

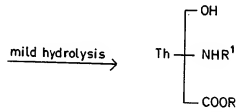
(3) Reaction of 1 with an alcohol such as methanol, ethanol or benzyl alcohol. This reaction may be conducted in the presence of a carbodiimide condensing agent such as dicyclohexylcarbodiimide. Suitable solvent, at a temperature of from 0°C to reflux for from 15 minutes to 18 hours, include $CHCl_3$, CH_2Cl and CH_2Cl_2.

(4) Reaction of an N-acylated acid anhydride of 1 prepared by reacting the free acid 1 with an acid chloride such as ethylchloroformate or benzylchloroformate with an alcohol such as those listed in (3) under the same conditions of reaction as given above for (3). The anhydride is prepared by reacting 1 and the acid chloride in a solvent such as tetrahydrofuran (THF) or CH_2Cl_2 at a temperature of from 25°C to reflux for from 16 minutes to 10 hours.

(5) Reaction of labile esters of 1 such as the trimethylsilyl ester or dimethyl - *t* - butylsilyl ester with RX' where X' is halogen such as bromo and chloro and R is as defined, in a solvent such as THF or CH_2Cl_2 at a temperature of from 0°C to reflux for from 15 minutes to 16 hours. For example according to the following scheme:



3

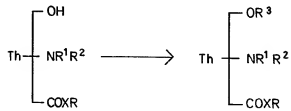


wherein TMS is triorganosilyl such as trimethylsilyl and all other symbolism is as previously defined.

The amides of the present invention are most conveniently prepared by reacting the acid anhydride of Ib (X =, R = acyl) with ammonia or with the desired amine, e.g., the alkyl, dialkyl or heterocyclic amines listed above.

The above-recited schemes of esterification are well known in the related bicyclic β-lactam antibiotic art and indeed in all of general organic synthesis: the reaction conditions are not critical.

Starting materials Ia and Ic are conveniently prepared by any of a variety of well known esterification or etherification reactions upon the secondary alcoholic group of 1b Such procedures include:



1b 2

1.) For the preparation of ethers of the present invention, the acid-catalysed reaction of 1b with a diazoalkane such as diazomethane, phenyldiazomethane or diphenyldiazomethane in an inert solvent such as dioxane, tetrahydrofuran (THF), halohydrocarbons such as CH_2Cl_2 or ethylacetate in the presence of a catalytic amount of a strong acid or Lewis acid such as toluenesulfonic acid, trifluoracetic acid, fluoboric acid or boron trifluoride and the reaction may be carried out at a temperature of from −78°C to 25°C for from a few minutes to 2 hours.

2.) For the preparation of ethers of the present invention, the reaction of 1b with an alkylating agent such as an active halide, for example methyl iodide, benzyl bromide or *m*-phenoxybenzyl bromide, or an alkylsulphonate such as dimethyl sulphate, diethyl sulphate or methyl fluorosulphonate in the presence of a strong base capable of forming the alcoholate anion of Ib. Suitable bases include alkali and alkaline-earth metal oxides and hydrous oxides, alkali metal alkoxides such as potassium tertiarybutoxide, tertiary amines such as triethylamine, alkali metal alkyls and aryls such as phenyllithium, and alkali metal amides such as sodium amide. Suitable solvents include any inert anhydrous solvent such as *t*-butanol, dimethylformamide (DMF), THF, hexamethylphosphoramide (HMPA) and dioxane and the reaction may be carried out at a temperature of from −78°C to 25°C. for from a few minutes to 4 hours.

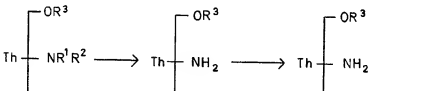
3.) For the preparation of esters of the present invention, the reaction of Ib with any of the above-listed acyl radicals in their acid form. This reaction may be conducted in the presence of a carbodiimide condensing agent such as dicyclohexylcarbodiimide. Suitable solvents include any inert solvent such as $CHCl_3$, CH_2Cl_2, DMF, HMPA, acetone or dioxane and the reaction may be carried out at a temperature of from 0°C. to 60°C. for from 15 minutes to 12 hours.

4.) For the preparation of esters of the present invention, the reaction of Ib with an acyl halide or an acid anhydride, wherein the acyl residue is described above. Generally, when the above-described acylating reaction involves an acid halide (suitable halides are chlorides, iodides, bromides) or an acid anhydride the reaction is conducted in an anhydrous organic solvent such as acetone, dioxane methylene chloride, chloroform or DMF in the presence of a suitable acceptor base such as $NaHCO_3$, MgO, triethylene or pyridine at a temperature of from 0°C. to 40°C. for from 1 to 4 hours.

Suitable acyl halides and anhydrides include acetic anhydride, bromoacetic anhydride, propionic anhydride, benzoylchloride, phenylacetyl chloride, azidoacetyl chloride, 2-thienylacetyl chloride, (2, 3 and 4)-nicotinyl chloride, *p*-nitrobenzoyl chloride, 2,6-dimethoxybenzoyl chloride, 4-guanidinophenylacetyl chloride, hydrochloride, methanesulfonyl chloride, dibenzylphosphorochloridate, dimethylthiophosphorochloridate, 2 - furoyl, ethyl carbonic anhydride, methylchloroformate, and *bis*(p-nitrobenzyl)phosphorochloridate.

5.) For the preparation of esters of the present invention, the reaction of *Ib* with a suitably substituted ketone or isocyanate such as ketene, dimethyl ketene, methylisocyanate, methylisothiocyanate, chlorosulfonyl isocyanate. Suitable solvents include dioxane, tetrahydrofuran, chloroform and the reaction may be carried out at a temperature of from −70°C. to 60°C . for from 15 minutes to 18 hours.

The intermediate compound 2 is then N-deblocked as described above to provide starting material Ic. From Ic, Ia is prepared by deblocking the carboxyl group:



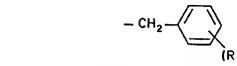
2 Ic Ia

Starting material Ia is conveniently and preferably obtained when X is oxygen and R is a readily removable carboxyl protecting or blocking group (see above).

Starting material Ia is prepared by deblocking according to any of a variety of well known procedures which include hydrolysis and hydrogenation. When the preferred carboxyl-blocking groups are used (below), the preferred deblocking procedure is hydrogenation, the intermediate compound (Ic or 2) being hydrogenated in a solvent such as a C_{1-4} alkanol in the presence of a hydrogenation catalyst such as palladium or platinum or an oxide thereof.

In this connection, it is noted that suitable "blocking groups" R include the sub-generic groups defined above as aralkyl, haloalkyl, alkanoyloxyalkyl, alkoxyalkyl, alkenyl, substituted alkyl, and aralkoxyalkyl, and also including alkylsilyl, where alkyl has 1—10 carbon atoms. For example, suitable "blocking groups" R include benzyl, phenacyl, *p*-nitrobenzyl, methoxymethyl, trichloroethyl, trimethylsilyl, tributyltin, *p*-methoxybenzyl and benzhydryl. These blocking groups are preferred since they are generally recognized easily-removable blocking groups in the cephalosporin and penicillin art.

The preferred carboxyl blocking groups, are benzyl and substituted benzyl of formula



where n is 0, 1 or 2 and R′ is C_{1-6} alkoxyl or nitro.

In the alternative it should be noted that the compounds of the present invention may be arrived at by operating uoon the N-alkylated thienamycin to achieve derivatization by establishment of R^3 and/or —COXR. Such procedure is exactly as described above except that the N-alkylated compound replaces the N-acylated compound and, of course, there is no need to N-deblock.

The products of this invention (II) form a wide variety of pharmacologically acceptable salts with inorganic and organic bases; these include, for example, metal salts obtained by reaction with alkali or alkaline-earth metal hydroxides, carbonates or bicarbonates and salts derived from primary, secondary or tertiary amines such as monoalkylamines, dialkylamines, trialkylamines, lower alkanolamines, di-(lower-alkanol)amines, lower alkylenediamines, N,N - diaralkyl lower alkylenediamines, aralkylamines, amino substituted lower alkanols, N,N-di-(lower alkyl)amino substituted lower alkanols, amino-, polyamino- and guanidino-substituted lower alkanoic acids and nitrogen-containing heterocyclic amines, where "lower" means "containing up to six carbon atoms". Representative examples include salts from sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium hydroxide, calcium carbonate, trimethylamine, triethylamine, piperidine, morpholine, quinine, lysine, protamine, arginine, procaine, ethanolamine, morphine, benzylamine, ethylenediamine, N,N′ - dibenzylethylenediamine, diethanolamine, piperazine, dimethylaminoethanol, 2-amino - 2 - methyl - 1 - propanol, theophylline and N - methylglucamine. Acid addition salts, e.g. with hydrochloric, hydrobromic, sulfuric, nitric, toluene - *p* - sulphonic and methane sulphonic acids may also be formed when a basic group is present in a substituent.

The salts can be mono-salts such as the monosodium salt obtained by treating one equivalent of sodium hydroxide with one equivalent of the product (II), also mixed di-salts. Such salts may be obtained by treating one equivalent of a base having a divalent cation, such as calcium hydroxide, with one equivalent of the product (II). The salts of this invention are pharmacologically acceptable nontoxic derivatives which can be used as the active ingredient in suitable unit-dosage pharmaceutical forms. Also, they may be combined with other drugs to provide compositions having a broad spectrum of activity.

Thienamycin derivatives of the present invention (including the enantiomers) are valuable antimicrobial substances which are active against various gram-positive pathogens such as *Streptomyces aureus*, *Streptomyces pyogenes* and *Bacillus subtilis*, *Salmonella schottmuelleri* and gram negative microorganisms such as *Escherichia coli*, *Preteus norganii*, *Klebsiela* and *Proteus vulgaris*. Thus, the free acid and especially the salts thereof such as amine and metal salts, particularly the alkali metal and alkaline earth metal salts, are useful bactericides and can be used for removing susceptible pathogens from dental and medical equipment, for separating microorganisms, and for therapeutic use in humans and animals. For this latter purpose pharmacologically acceptable salts with inorganic and organic

bases such as those known and used for the adminstration of penicillins and cephalosporins can be utilized. For example, salts such as alkali metal and alkaline-earth metal salts, and primary, secondary and tertiary amine salts can be used for this purpose. These salts can be combined with pharmaceutically acceptable liquid and solid vehicles to form suitable dosage unit forms such as pills, tablets, capsules, suppositories, syrups and elixirs, which can be prepared in accordance with well known procedures.

The novel compounds are valuable antibiotics active against various gram-positive and gram-negative bacteria, and accordingly, find utility in human and veterinary medicine. The compounds of this invention can therefore be used as antibacterial drugs for treating infections caused by gram-positive or gram-negative bacteria, for example against *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae. Bacillus subtilis, Salmonella typhosa, Pseudomonas* and *Bacterium proteus*. The antibacterials of the invention may further be utilized as additives to animal feedingstuffs, for preserving foodstuffs and disinfectants. For example, they may be used in aqueous compositions in concentrations ranging from 0.1 to 100 parts of antibiotic per million parts of solution in order to destroy and inhibit the growth of harmful bacteria on medical and dental equipment and as bactericides in industrial applications, for example in water-based paints and in the white water of paper mills to inhibit the growth of harmful bacteria.

The products of this invention may be used alone or in combination as an active ingredient in any one of a variety of pharmaceutical preparations. These antibiotics and their corresponding salts may be used in capsule form or as tablets, powders or liquid solutions or as suspensions or elixirs. They may be administered orally, intravenously or intramuscularly.

The compositions are preferably presented in a form suitable for absorption by the gastro-intestinal tract. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; lubricants, for example, magnesium stearate, talc, polyethylene glycol, silica; disintegrants, for example, potato starch or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to well known methods. Oral liquid preparations may be in the form of aqueous or oily suspension, solution, emulsions, syrups or elixirs or may be presented as a dry product, for reconstitution with water or other suitable vehicles before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxy-ethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible oils, for example almond oil, fractionated coconut oil, oily esters, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxy-benzoates or sorbic acid. Suppositories will contain conventional suppository bases, e.g. cocoa butter or other glyceride.

Compositions for injection may be presented in unit dose form in ampoules, or in multidose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compositions may also be prepared in suitable forms for absorption through the mucous membranes of the nose and throat or bronchial tissues and may conveniently take the form of powder or liquid sprays or inhalants, lozenges, or throat paints. For medication of the eyes or ears, the preparations may be presented as individual capsules, in liquid or semi-solid form, or may be used as drops. Topical applications may be formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints and powders.

Also, in addition to a carrier, the compositions may include other ingredients such as stabilizers, binders, antioxidants, preservatives, lubricators, suspending agents, viscosity agents or flavoring agents. In addition, there may also be included in the composition other active ingredients to provide a broader spectrum of antibiotic activity.

For veterinary medicine the composition may, for example be formulated as an intramammary preparation in either long acting or quick-release bases.

The dosage to be administered depends to a large extent upon the condition of the subject being treated and the weight of the host, the route and frequency of

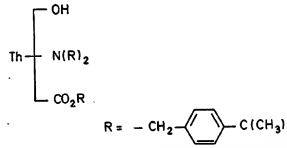
administration, the parenteral route being preferred for generalized infections and the oral route for intestinal infections. In general, a daily oral dosage consists of from about 15 to about 600 mg. of active ingredient per kg. of body weight of the subject in one or more applications per day. A preferred daily dosage for adult humans lies in the range of from about 80 to 120 mg of active ingredient per kg. of body weight.

The compositions may be administered in several unit dosage forms as, for example, in solid or liquid orally ingestible dosage form. The compositions per unit dosage, whether liquid or solid, may contain from 0.1% to 99% of active material, the preferred range being from about 10—60%. The composition will generally contain from 15 mg. to 1500 mg. of the active ingredient; however, in general, it is preferable to use a dosage in the range of from 250 mg. to 1000 mg. In parenteral administration the unit dosage is usually the pure compound in a slightly acidified sterile water solution or in the form of a soluble powder intended for solution.

The following Examples, illustrate but do not limit the present invention. Certain Examples are concerned with the preparation of starting materials. The words "Porasil", "Dowex", "Teflon", "Supercel", "Linde", "Celite", "Branson", "Sonifier" and "Difco" are trade marks, proportions of liquid mixtures are given on a volume basis and "ϕ" has its well known meaning of phenyl.

Example 1.

Preparation of N,N - di - *p* - *t* - Butylbenzyl - thienamycin - *p* - *t* - butylbenzyl ester



Thienamycin, 40 mg., is stirred for 3½ hours in 0.6 ml. HMPA with 0.0275 ml. *p* - *t* - butylbenzyl bromide. The thienamycin goes into solution within 30 minutes. The reaction mixture is diluted with ethylacetate (EtOAc), and washed successively with aqueous K_2HPO_4, water (2x) and brine. The EtOAc layer is dried with $MgSO_4$, filtered and evaporated. The residue is chromatographed by TLC on silica gel, eluting with 5% MeOH in $CHCl_3$. Pure title compound, 4 mg., is obtained at Rf *ca.* 0.6. IR (μ, film):
3.0, OH; 5.62, β-lactam; 5.90, ester NMR ($CDCl_3$):
1.29 (s, *t*-Bu), 2.6—3.3 (m, CH_2's), 3.57 (s, NCH_2),
3.8—4.4 (m, β-lactam CH's), 5.23 (s, OCH_2), 7.29 (s, aryl).
MS: m/e 710, 666, 624, 367, 335, 322.

Following the above procedure, but substituting for *p* - *t* - butylbenzyl bromide an equivalent amount of *p* - methoxybenzylbromide, there is obtained N,N - *Bis* - *p* - methoxybenzyl thienamycin *p* - methoxybenzyl ester.

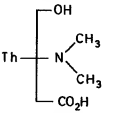
Example 2.

N - p - nitrobenzyl thienamycin p - nitrobenzyl ester and N,N - bis p - nitrobenzyl thienamycin p - nitrobenzyl ester

To a solution of thienamycin (71 mg.) in 2 ml of dimethylsulfoxide is added a solution of 27 mg of triethylamine in 0.27 ml of methylene chloride followed by 56 mg of *p* - nitrobenzyl bromide. The mixture is stirred for 1/2 hour at 25°C., then 7 ml of methylene chloride and 7 ml of 0.1*M* pH 9 buffer are added. The organic phase is separated, washed with water and with brine and then evaporated. The residue is chromatographed on a 1,000μ 8" × 8" silica plate developed with ethyl acetate. The band at 0.5—2.5 cm is extracted with ethylacetate yielding N - *p* - nitrobenzyl thienamycin *p* - nitrobenzyl ester in UV λ_{max} 267 mμ Sh 320 mμ. Relative absorbance 3:2. The band at 4.5—7 cm yields N,N-bis-p-nitrobenzyl thienamycin p-nitrobenzyl ester. UV λ_{max} 267 mμ Sh 320 mμ. Relative absorbance 2:1.

Example 3.

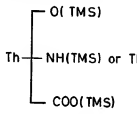
Preparation of N,N - Dimethyl thienamycin



Thienamycin (12.7 mg) is dissolved in 2 ml of an aqueous formaldehyde solution (0.07%) and hydrogenated at 40 psi using platinum oxide (14 mg) catalyst. After four hours, the solution is adjusted to pH 7.0 and chromatographed on a column of XAD—2 resin (15 ml.). The column is eluted with water. A fraction is collected containing a mixture of thienamycin and N,N - dimethyl thienamycin. Analytical high pressure liquid chromatography on C_{18} Porasil with 10% tetrahydrofuran in water as solvent shows two peaks with retention times of 1.75 and 2.5 minutes.

Example 4.

(This is a preparation of a starting material)



TMS = trimethylsilyl

Preparation of Silylated thienamycin

Thienamycin (80.0 mg.) is suspended in 40 ml. tetrahydrofuran (THF) under a N_2 atmosphere and is concentrated to 10 ml., hexamethyldisilazane (1.0 ml) and trimethylchlorosilane (300 μl) is added. The mixture is reacted for 20 mins. at 25°C., with vigorous stirring. The suspension is then centrifuged to remove ammonium chloride. The supernatant is evaporated to an oil under a nitrogen stream for future reaction.

Example 5.

Preparation of N - Methyl - thienamycin

Th(TMS)$_2$, prepared from 20 mg. of Thienamycin is dissolved 1 ml. of tetrahydrofuran. Dimethyl sulfate (15 mg.) is added and the mixture is stirred at 23°C. for 2 hours. Phosphate buffer (pH 7, 1 ml) is added and the mixture adjusted to pH 4 and stirred for 15 minutes. The mixture is adjusted to pH 7 and extracted with ethyl acetate. The aqueous layer is separated and applied to a column (40 ml) XAD—2 resin. The column is eluted with water and the effluent is monitored by refractive index and U.V. absorbance; initial fractions containing inorganic salts are discarded; the portions containing N - methyl thienamycin are evaporated to a small volume and freeze-dried.

Example 6.

N - Methyl thienamycin

A mixture of thienamycin (272 mg) and trimethylsilyl imidazole (280 mg) in 20 ml of THF is stirred at 25°C., for 30 minutes. *p* - Nitrobenzaldehyde (120 mg.) and powdered anhydrous magnesium sulfate (0.5 g) are added and the solution is evaporated under reduced pressure to 2 ml. The solution is stirred at 25°C., for 4 hours. To the resulting solution of O-trimethylsilyl N - *p* - nitrobenzylidene thienamycin trimethylsilyl ester is added 150 mg of dimethyl sulfate and the

mixture is stirred at 25°C. for one hour. The mixture is poured into 10 ml of 0.1*N* pH 6 phosphate buffer and after stirring for 15 minutes, extracted with ether. The aqueous phase is chromatographed on 200 g of XAD—2 resin. Elution with water yields a fraction containing N - methyl thienamycin, which is concentrated and freeze-dried.

Example 7.

Preparation of Thienamycin Benzyl Ester

This is a starting material (see the specification of our copending application No. 48236/76 (Serial No. 1570986).

Step A: N - (p - Nitrobenzyloxycarbonyl) - thienamycin Sodium salt

To thienamycin (43 mg.) at 0°C., is added 10 ml., 1:1 tetrahydrofuran (THF):Water. The mixture is rapidly stirred while 102 mg. $NaHCO_3$ (10 equivalents) is added, and then, dropwise with stirring over 2 minutes, four equivalents of *o* - nitrobenzylchloroformate is added. After 30 minutes, the pH is adjusted to 7 with aqueous 25% H_3PO_4 and the solution extracted 3X with ether. The aqueous portion is adjusted to pH 2.2 at 0°C; 500 mg. solid NaCl is added. The cold acidic solution is extracted 3X with cold EtOAc. The EtOAc extracts are combined and quickly back-washed with cold brine, dried with $MgSO_4$, filtered and back-extracted with 10 ml of water containing 1.75 equivalents of solid $NaHCO_3$. The extract is lyophilized *in vacuo* at 20°C. to provide the title compound.

Step B: N - (p - Nitrobenzyloxycarbonyl) - thienamycin Benzyl Ester

The product of Step A in 7.5 ml EtOAc is treated with an excess of phenyldiazomethane (4 ml. of a solution comprising 20 mg/ml. ether) at 4°C for 2 hours. The mixture is concentrated to wet residue at 20°C under reduced pressure. The desired compound is isolated by thin-layer chromatography, eluting with EtOAc: ether (9:1) to afford 17.5 mg. of N - (*p* - nitrobenzyloxycarbonyl) - thienamycin benzyl ester.

Step C: Thienamycin Benzyl Ester

The compound of Step B is dissolved in ethyl alcohol, 35 mg. PtO_2 is added and the mixture is hydrogenated at 50 lbs. pressure for 45 min. The reaction mixture is centrifuged, liquid decanted and evaporated, and subjected to preparative thin layer chromatography on silica gel, eluting with 1:4 methanol: $CHCl_3$.

Example 8.

Preparation of N,N - Dimethyl-thienamycin

A mixture of thienamycin benzyl ester (18 mg.), methyl iodide (14 mg.) and MgO (4 mg.) in 2 ml. of hexamethyl phosphoramide is stirred at 25°C. for one hour. The mixture is poured into hexane yielding a precipitate of crude N,N - dimethyl thienamycin benzyl ester, which is taken up in ethyl acetate and purified by thin-layer chromatography on silica gel.

A solution of 10 mg. of N,N - dimethyl thienamycin benzyl ester in 1 ml. of dioxane-water, 4:1, is hydrogenated at 40 psi in the presence of 10 mg. of palladium oxide for 2 hours. The catalyst is removed by filtration and the filtrate is shaken with a mixture of 5 ml. of ethyl acetate and 5 ml. of 0.01*N* pH 7 phosphate buffer. The aqueous phase is separated, evaporated to a small volume and freeze-dried, yielding N,N - dimethyl thienamycin.

Example 9.

N - Benzyl and N,N - Dibenzyl - thienamycin

A mixture of thienamycin (150 mg), benzyl bromide (300 ml) and sodium bicarbonate (200 mg) in 10 ml of 80% aqueous ethanol is stirred at 23°C for 5 hours. The solution is evaporated under reduced pressue to 2 ml, diluted with 5 ml of water and extracted with ether. The aqueous layer is chromatographed on a column of 100 ml of XAD—2 resin. Elution with water removes unreacted thienamycin. Elution with increasing concentrations of tetrahydrofuran (THF) gives a fraction containing N - benzyl thienamycin and subsequently a fraction containing N,N - dibenzyl thienamycin, which are recovered by lyophilization.

Following the above procedure but substituting for the benzyl bromide an equivalent amount of allyl bromide, there are obtained N - allyl and N,N - diallyl thienamycin.

Example 10.

N - Ethyl - N,N - bis - *p* - methoxybenzyl - thienamycin *p* - methoxybenzyl ester Iodide

A solution of 100 mg of N,N - bis - *p* - methoxybenzyl thienamycin *p* - methoxybenzyl ester and 0.5 ml of ethyl iodide in 1 ml of dimethylformamide (DMF) is stirred at 25°C. for 2 hours. The excesses of reagents and solvent are removed under reduced pressure and the residue is triturated with ether to give the solid product.

Example 11

N - Ethyl thienamycin

A solution of 120 mg of N - ethyl - N,N - bis - *p* - methoxybenzyl thienamycin *p* - methoxyethyl ester iodide in 5 ml of 80% aqueous ethanol containing 20 mg of sodium bicarbonate is hydrogenated in the presence of 100 mg of palladium oxide at 40 psig for 4 hours at 25°C. The catalyst is removed by filtration and the filtrate is evaporated to 2 ml, diluted with 5 ml of water and extracted with ether. The aqueous phase is chromatographed on 100 ml of XAD-2 resin. Elution with water yields N-ethyl thienamycin, which is recovered by lyophilization.

Example 12.

N,N - Dimethyl N - Benzyl - thienamycin

A solution of N - benzyl thienamycin (200 mg) in 5 ml of 50% aqueous dioxane is titrated to pH 8.4. Dimethyl sulfate (0.5 ml) in 2 ml of dioxane is added with stirring during 10 minutes. The pH is maintained at 8.4 by the addition of 1.0*N* sodium hydroxide by means of an automatic titrator. The mixture is stirred an additional hour then diluted with 10 ml of water, adjusted to pH 7 and extracted with ether. The aqueous phase is concentrated to 5 ml and chromatographed on 200 ml of XAD-2 resin. The column is eluted with water followed by 20% aqueous THF. The N,N - dimethyl - N - benzyl - thienamycin (an internal salt) is recovered from the THF eluate by lyophilization.

Example 13.

N,N - Dimethyl - thienamycin

A solution of N,N - dimethyl - N - benzyl - thienamycin is hydrogenated following the procedure of Example 11 yielding N,N - dimethyl - thienamycin.

Example 14.

N - Salicylidene - thienamycin benzyl ester

This compound can be used as a starting material and is claimed in the specification of our copending application No. 48240/76. (Serial No. 1570990)

Thienamycin (115 mg) is dissolved in 4 ml of 50% aqueous dioxane. The solution is cooled to 0°C. and titrated to pH 5 with *N* sulfuric acid. Phenyldiazomethane (60 mg) in 0.9 ml of dioxane is added during 5 minutes with vigorous stirring while the pH is maintained at 5—5.5 under control of a pH state. After reacting an additional 5 minutes the mixture is extracted with ether. The aqueous layer is adjusted to pH 8.3 with sodium bicarbonate solution and extracted with ethyl acetate. To the solution containing thienamycin benzyl ester is added 35 μl of salicylaldehyde and anhydrous magnesium sulfate. The solution is concentrated to 1 ml on the rotary evaporator and allowed to stand at 25°C. for one hour. The course of the reaction is followed by TLC on silica gel in 20% methanol in chloroform. A new spot at Rf 0.8 appears. The product is isolated by preparative TLC in 50:50 ethyl acetate:chloroform and appears as a yellow band at Rf 0.32; U.V. λ_{max} 259 mμ and 322 mμ of equal intensity. d(CH_3CHOH); 6.7—7 and 5.7—6.4 (multiplets); 4.72 ,s,(OCH_2); 2.5—7.5 (multiplex aromatic H) and 1.75 , S, (C = N) H

Following the above procedure but substituting diphenyl diazomethane for phenyldiazomethane there is obtained salicylidene thienamycin benzhydryl ester NMR 8.67 H

d(CH_3COH) 5.65—7.1 (aliphatic multiplex); 2.5—3.2 (aromatic multiplex) 1.67 (C = N) H

Following the above procedure but substituting *p* - nitro benzaldehyde for salicylaldehyde there are obtained *p* - nitrobenzylidene thienamycin benzyl ester and the corresponding benzhydryl ester. TLC 5:1 $CHCl_3$ EtOH Rf 0.8. Similarly, when benzaldehyde, *p* - bromobenzaldehyde, *p* - dimethylaminobenzaldehyde,

5,5 - dimethyl - 1,3 - cyclohexanedione, dimethylaminoacetaldehyde, and isobutyraldehyde are substituted for salicyaldehyde the corresponding benzhydryl and benzyl esters are obtained.

Example 15.

N - Ethyl N - p - bromobenzylidene thienamycin benzyl ester Ethylsulfate

This compound can be used as a starting material and is claimed in the specification of our copending application No. 48240/76.

p - Bromobenzylidene thienamycin benzyl ester (200 mg) is dissolved in 2 ml of methylene chloride and 0.2 ml of diethyl sulfate is added. The solution is stirred at 40° for 5 hours; 20 ml of ether is added and the precipitate, N - ethyl - N - *p* - bromobenzylidene thienamycin benzyl ester ethylsulfate, is recovered by filtration.

Example 16.

N - Ethyl - thienamycin

A solution of N - ethyl - N - *p* - bromobenzylidene thienamycin ethyl sulfate (200 mg) in 5 ml of 80% ethanol containing 40 mg of sodium bicarbonate is hydrogenated in the presence of 0.2 g of palladium oxide at 40 psig for 4 hours. The catalyst is removed by filtration. The filtrate is evaporated to 2 ml, diluted with 5 ml of water and extracted with ether. The aqueous phase is chromatographed on 200 ml of XAD-2 resin. The column is eluted with water and the fractions containing N - ethyl thienamycin are lyophilized.

Example 17.

N - Methylthienamycin Benzyl Ester

A solution of N - methylthienamycin (50 mg) in 1 ml of water and 1 ml of dioxane is cooled to 0° and adjusted to pH 5 with *N* sulfuric acid. Phenyldiazomethane, (37 mg) in 0.5 ml of dioxane is added during 5 minutes while the pH is maintained at 5 to 5.5 by means of an automatic titrator. The mixture is diluted with water (5 ml) and extracted with ether. The aqueous phase is overlayered with ethyl acetate, cooled and adjusted to pH 2.5. The ethyl acetate is separated by centrifugation and the aqueous phase is adjusted pH 8.0 with sodium bicarbonate and extracted twice with ethyl acetate. The extracts are combined and evaporated and the product is isolated by preparative thin-layer chromatography on silica gel using 5:1 chloroform:methanol solvent.

Following the above procedure but starting with N,N - dimethyl - thienamycin, there is obtained N,N - dimethyl - thienamycin benzyl ester.

Example 18.

N - o - Hydroxybenzyl - thienamycin Benzyl Ester

A solution of N - salicylidene - thienamycin benzyl ester (40 mg) in 1 ml of dioxane is hydrogenated at 40 psig and 23°C. in the presence of 10 mg of platinum oxide for 2 hours. The catalyst is removed by filtration and the filtrate is evaporated. The residue is taken up in chloroform and chromatographed on silica gel affording essentially pure N - orthohydroxybenzyl thienamycin benzyl ester.

Following the above procedure except replacing the N - salicylidene thienamycin benzyl ester with an equivalent amount of N - benzylidene thienamycin benzyl ester, N - *p* - bromobenzylidene thienamycin benzyl ester, N - dimethylaminobenzylidene thienamycin benzyl ester, N - dimethylaminoethylidene thienamycin benzyl ester, and N - 2 - methylpropylidene thienamycin benzyl ester, there are obtained, respectively, N - benzyl thienamycin benzyl ester, N - *p* - bromobenzyl thienamycin benzyl ester, N - *p* - dimethylaminobenzyl thienamycin benzyl ester, N - dimethylaminoethyl thienamycin benzyl ester, and N - isobutyl thienamycin benzyl ester.

Example 19.

N,N,N - Trimethyl - thienamycin

A solution of Thienamycin (150 mg) in 7.5 ml of 0.1*N* pH 7 phosphate buffer and 7.5 mlo of dioxane is adjusted to pH 8.4. Dimethyl sulfate (1 ml) is added and the solution is rapidly stirred for 40 minutes while the pH is maintained at 8.4 by the addition of *N* sodium hydroxide solution. The solution is extracted twice with ether. The aqueous phase is evaporated to 4 ml and applied to a column (200 ml) of XAD-2 resin. The column is eluted with water and the progress of the separation is followed by high pressure liquid chromatography on C^{18} Bondapak resin using 10%

aqueous acetonitrile. The retention time of the product is 1.2 x thienamycin. The fractions containing the product are combined, concentrated and freeze-dried giving 41 mg of N,N,N' - trimethyl thienamycin, which is an internal salt. Electrophoresis (50 V/cm, 2 hrs, pH 7 buffer) shows a bioactive zone which moves 6 cm towards the cathode. The NMR spectrum (60MHZ, D_2O) shows a strong methyl singlet at 6.78 τ with an integral 3X the side chain methyl doublet at 8.7 τ U.V.$_{\lambda max}$ 298 $n\mu$, E%185.

Following the above procedure but using 0.25 ml of dimethylsulfate and allowing the reaction to proceed for only 15 minutes, there is obtained a mixture containing N - methyl and N,N - dimethyl thienamycin, which is separated by column chromatography.

Example 20.

Preparation of N,N,N - Trimethyl - thienamycin

A suspension of N,N - dimethyl thienamycin (20 mg.), in 10 ml. of tetrahydrofuran is stirred under a nitrogen atmosphere and hexamethyl disilizane (0.2 ml.) and trimethyl chlorosilane (0.1 ml.) are added. The mixture is stirred vigorously at 23°C. for 20 minutes and then centrifuged, and the supernatant solution is evpaorated under reduced pressure. The residual oil is dissolved in THF (1 ml), methyl iodide (0.05 ml) is added with vigorous stirring and the mixture is stirred for 30 minutes. Ethyl acetate, 5 ml., and 0.1*N* pH 4 phosphate buffer (5 ml) are added, and stirring is continued for 15 minutes at 25°C. The mixture is adjusted to pH 7 and separated. The aqueous layer is concentrated to 1 ml. and applied to a column of XAD-2 resin (20 ml.). Elution with water, followed by 10% tetrahydrofuran, yields a fraction containing N,N,N - trimethyl thienamycin, which is freeze-dried to give a solid product.

Example 21.

N,N - Dimethylthienamycin pivaloyloxymethyl ester

A solution of N,N - dimethylthienamycin (30 mg) and pivaloyloxymethyl bromide (25 mg) in 0.2 ml of hexamethylphosphoramide is stirred at 23°C. for one hour. Ethyl acetate (5 ml) is added and the mixture is extracted successively with aqueous sodium bicarbonate solution, water and saturated sodium chloride solution. The organic phase is dried and evaporated to a small volume and chromatographed on 8" × 18" 1000μ silica plate using 5:1 chloroform-methanol solution. The band containing N,N - dimethyl thienamycin pivaloyloxymethyl ester is scraped off and eluted with ethyl acetate.

Example 22.

N,N, - Dimethylthienamycin 3 - methyl - 2 - butenyl ester hydrochloride

To a solution of N,N - dimethyl thienamycin (30 mg) in 0.5 ml of 3 - methyl - 2 - butenyl alcohol containing 3.6 mg of hydrogen chloride is added 21 mg of dicyclohexyl carbodiimide. The solution is stirred at 23° for one hour and then filtered from dicyclohexyl urea. The filtrate is evaporated and the residue triturated with ether leaving a solid containing N,N - dimethyl thienamycin 3 - methyl - 2 - butenyl ester hydrochloride.

Following the above procedure but substituting methylthioethanol for 3 - methyl - 2 - butenol there is obtained N,N - dimethyl thienamycin methylthioethyl ester.

Example 23.

O - Acetyl - N,N - Dimethyl - thienamycin

N,N - Dimethyl thienamycin (100 mg) is added to a mixture of 0.3 ml of acetic anhydride in 1 ml of pyridine. The mixture is allowed to react at 23°C for three hours then pumped to dryness under vacuum. The solid residue is dissolved in water and chromatographed on 100 ml of XAD-2 resin. After elution with water the product is eluted with 10% THF. The fractions containing O - acetyl - N,N - dimethyl - thienamycin are combined, evaporated and freeze-dried.

Example 24.

Thienamycin Benzyl Ester

(This compound is a starting material)

A solution of Thienamycin (47 mg) in 1 ml of water and 1 ml of dioxane is cooled to 0°C and adjusted to pH 5 with *N* sulfuric acid. Phenyldiazomethane (37.2 mg) in 0.5 ml of dioxane is added during 2 minutes while the pH is maintained at 5

by means of an automatic titrator. After an additional 5 minutes, water (5 ml) is added and the mixture is extracted with ether. The aqeous phase is layered with ethyl acetate, cooled and adjusted to pH 2.5. The ethyl acetate phase is removed and the aqueous phase is adjusted to pH 8 with sodium bicarbonate and extracted twice with ethyl acetate. The latter ethyl acetate extracts are combined and dried over anhydrous magnesium sulfate. TLC on silica gel in 1:5 methanol chloroform shows a single ninhydrin-positive spot at Rf 0.24. The U.V. of the ethyl acetate solution shows a λ_{max} at 318 mμ with an optical density of 250.

Example 25.

N,N - Dimethyl - O - Sulfo - thienamycin benzyl Ester

To a solution of N,N - dimethyl - thienamycin benzyl ester (39 mg) in 0.3 ml of pyridine is added sulfur trioxide - pyridine (17 mg). The mixture is stirred at 25°C. for three hours and the excess of pyridine is evaporated under reduced pressure. The residue is taken up in 5 ml of water containing 10 mg of sodium bicarbonate and extracted once with ethyl acetate. The aqueous solution is concentrated to 2 ml. and chromatographed on 50 g of XAD-2 resin. The fractions containing N,N - dimethyl - O - sulfo - thienamycin benzyl ester are combined, concentrated and freeze-dried.

Example 26.

N,N - Dimethyl - O - sulfo - thienamycin sodium salt

A solution of N,N - dimethyl - O - sulfo - thienamycin benzyl ester (24 mg) in 1 ml of water containing 5 mg of sodium bicarbonate is hydrogenated in the presence of 20 mg of palladium oxide at 23°C at 1 atm pressure for 2 hours. The catalyst is removed by filtration and the filtrate is chromatographed on 20 g of XAD-2 resin. The fractions containing N,N - dimethyl - O - sulfo - thienamycin sodium salt are combined, concentrated and freeze-dried.

Example 27.

O - Formyl - N,N - dimethyl - thienamycin benzyl ester

To a solution of N,N - dimethyl thienamycin benzyl ester (100 mg) in 1 ml of pyridine is added a mixture of 100 mg of formic acid and 200 mg of acetic anhydride. The mixture is stirred for 2 hours at 25°C., and the excesses of reagents are removed under reduced pressure. The residue is taken up in ethyl acetate and the product is recovered by thin-layer chromatography on silica gel using 1:1 ethyl acetate:chloroform solvent.

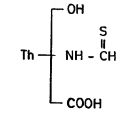
Example 28.

O - Formyl - N,N - Dimethyl - thienamycin

A solution of O - Formyl N,N - dimethyl thienamycin benzyl ester (50 mg) in 2 ml of 90% ethanol is hydrogenated in the presence of 50 mg of 10% palladium or charcoal at 23°C. and 1 atm. for 4 hours. The catalyst is removed by filtration The filtrate is evaporated and the residue, which contains O - Formyl - N,N - dimethyl thienamycin, is purified by chromatography on XAD-2 resin.

Example 29.

Preparation of N - Thioformyl - thienamycin

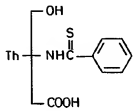


This is a starting material (see also the specification of application No. 48236/76 (Serial No. 1570986)).

Silylated thienamycin [Th(TMS$_2$), from 100 mg thienamycin, Example 4] is dissolved in dichloromethane (9 ml) in a stoppered flask under positive nitrogen pressure. To the magnetically stirred solution is added a solution of triethylamine

(60 μl) in dichloromethane (1 ml). This is followed by the addition of ethyl thioformate (100μl). After 1 hour the reaction solution is rapidly added to a stirred solution of pH 4 0.1*N* phosphate buffer (20 ml). The mixture is stirred for 5 minutes and the pH of the mixture adjusted to 7.0 with 1*N* NaOH. The aqueous phase is separated, washed with ethyl acetate (2 × 20 ml) and cooled in an ice bath. The solution is layered with ethyl acetate (15 ml) and the pH of the stirred mixture is adjusted to 3.5 with 1*N* phosphoric acid. The organic phase is separated and the buffered aqueous solution washed with ethyl acetate (2 × 15 ml). The combined ethyl-acetate washings are concentrated to half volume and layered with water (10 ml). Solid sodium bicarbonate is added until the pH of the mixture is 7.0. The aqueous phase is separated and lyophilized to give the sodium salt of N - thioformyl thienamycin.

Example 30



N - (Thiobenzoyl)thienamycin

This is a starting material (see also the specification of application No. 48236/76 (Serial No. 1570986)).

A solution of 55.8 mg (0.2 mmole) of thienamycin in 18 ml. of dioxane-water (1:1) is treated with 263 mg. (3.1 mmoles) of $NaHCO_3$ and cooled to 0°C. Two 200-μl portions of a solution of 100 mg of thiobenzoyl chloride in 0.6 ml of dry dioxan are added to the rapidly stirred reaction solution at 15-min. intervals. Each portion of acid chloride solution contains 0.2 mmole of thiobenzoyl chloride. Fifteen minutes after the second addition, the reaction solution is washed with two 8-ml. portions of ether. Ethyl acetate (8 ml) is added to the aqueous phase, which is adjusted to pH of 2.2 at 0°C. with rapid stirring using 20% H_3PO_4. The layers are separated and the aqueous layer is washed with 3 ml. of ethyl acetate. The combined ethyl-acetate layers are dried ($MgSO_4$). After separation of the drying agent, 10 ml of water is added to the ethyl-acetate solution and the product is extracted into the aqueous phase by adding 50 mg. (0.62 mmole) of $NaHCO_3$ with stirring at 0°C (pH 7.4). The layers are separated and an aqueous phase containing N - (thiobenzoyl) - thienamycin sodium salt is obtained and freeze-dried. Nmr in

$$\text{S} \quad -$$
$$\parallel$$

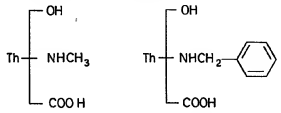
D_2O: δ7.3—7.9 characteristic of the C_6H_5 C-residue.

Example 31.

Preparation of N - Methyl - thienamycin (I) and N - Benzyl - thienamycin (II)

A mixture of N - (thioformyl)thienamycin (100 mg) and neutral Raney nickel (0.5 g) in 100 ml of 90% aqueous ethanol is stirred at 23°C for two hours. The nickel is removed by filtration and the filtrate is chromatographed on a column (100 ml) of Dowex 50 × 4, Na^- form (400 mesh) resin. The column is eluted with water and the fractions containing N - methyl thienamycin are combined and lyophilized.

Following the procedure of Example 31 except that an equivalent amount of N - (thiobenzoyl)thienamycin is substituted for the N - (thioformyl)thienamycin, there is obtained N - benzyl thienamycin.

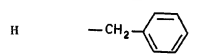
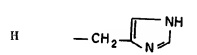


I II

Example 32.

Following the procedures set out in the foregoing Examples and text, the following compounds of Formula II are obtained. In compounds 2, 4 and 12 an internal salt is formed with the carboxylic residue, (R being H and X being O in all three of these compounds): in compound 3 an internal salt is formed with the sulfo radical R^3. Compound 15 is a bisulfate salt. The expression "ϕ" has its usual meaning of phenyl.

Compound	X	R^3	R	R^5	R^6	R^7	Q
1.)	O	H	$-CH_2-O-\overset{\overset{O}{\|}}{C}-CH_3$	CH_3	CH_3	CH_3	Cl
2.)	O	CH_3	–	CH_3	CH_3	CH_3	–
3.)	O	SO_3H	Na	CH_3	CH_3	CH_3	–
4.)	O	H	–	CH_3	CH_3	C_2H_5	–
5.)	O	H	H	C_2H_5	CH_3	–	–
6.)	O	H	H	C_2H_5	C_2H_5	–	–
7.)	O	H	$-CH_2-O-CH_2C(CH_3)_3$	$-CH_2CH=CH_2$	H	H	Cl
8.)	O	H	H	$-CH_2CH_2CH_3$	H	–	–
9.)	O	H	H	$-CH\phi_2$	H	–	–
10.)	O	H	H	$-CH\phi_2$	CH_3	–	–
11.)	O	H	H	$-C-\phi_3$	CH_3	–	–
12.)	O	H	–	$CH\phi_2$	CH_3	CH_3	–
13.)	O	H	$-CH_2-CH=CH_2$	$-CH_2-CH=CH_2$	H	H	Cl
14.)	O	H	$-CH_2-\overset{\overset{CH_3}{\|}}{C}=CH_2$	$-CH_2-\overset{\overset{CH_3}{\|}}{C}=CH_2$	H	H	Cl

Compound	X	R^3	R	R^5	R^6	R^7	Q
15.)	O	H	$-CH_2CH_2N(C_2H_5)_2$	CH_3	H	H	HSO_4
16.)	O	$-CH_2OCH_3$	*p*-nitrobenzyl	$-CH_2OCH_3$	$-CH_2OCH_3$	–	–
17.)	S	H	$-CH_2CH_2CH_3$	$-CH_2CH=CHCH_3$	H	H	Cl
18.)	O	H	H	$-CH_2CH_2CH=CH_2$	H	–	–
19.)	O	H	H		H	–	–
20.)	O	$-COOCH_3$	H		H	–	–
21.)	O	H	H	$-CH_2CH_2CH_2CH_2-$	–	–	–
22.)	O	H	$-CH_2-CH_2N-(CH_3)_2$	$-CH_2CH_2-N-(CH_3)_2$	H	H	HPO_4
23.)	O	H	H	$-CH_2-C-CH_3$	H	–	–
24.)	O	H	H	$-CH_2CH_2(OCH_3)_2$	H	–	–
25.)	O	H	H	$-CH_2-C\equiv CH$	H	–	–
26.)	O	H	H	$-CH_2CH_2O-CH_2CH_2-$	–	–	–

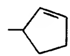
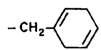
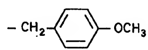
Compound	X	R^3	R	R^4	R^5	Q
27.)	O	H	$-CH_2C-\phi$ (O)	$-CH_2C-\phi$ (O)	CH_3	–	–
28.)	O	H	CH_2S-CH_3	$-CH_2SCH_3$	$-CH_2SCH_3$	–	–
29.)	O	H	$-CH_2-O-C(CH_3)_3$ (O)	$-CH_2-O-C(CH_3)_3$ (O)	H	–	–
30.)	O	H	H	$-CH_2CH_2-C-OCH_3$ (O)	H	–	–
31.)	O	H	H	CH_3	$-CH_2-CH=CH-C_2H_5$	–	–
32.)	O	H	H		H		–
33.)	O	$-C-CH_2NH_2$ (O)	H	$-C_2H_5$	$-C_2H_5$	H	CH_3COO
34.)	O	H	H			–	–
35.)	O	H	H	$-CH(CH_3)_2$	H	–	–

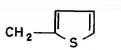
Compound	X	R^3	R	R^5	R^6	R^7	Q
36.)	O	H	H	$-CH_2CH_2CH_2CH_3$	H	–	–
37.)	O	H	H	$-CH_2CH(CH_3)-CH_3$	H	–	–
38.)	O	H	H	$-CH(CH_3)CH_2CH_3$	H	–	–
39.)	O	H	H	$-CH_2CH_2CH_2CH_2CH_3$	H	–	–
40.)	O	H	H	$-CH(CH_3)-CH_2CH_2CH_3$	H	–	–
41.)	O	H	H	$-CH_2CH(CH_3)-CH_2CH_3$	H	–	–
42.)	O	H	H	$-CH_2CH_2CH(CH_3)-CH_3$	H	–	–
43.)	O	H	H	$-CH(CH_3)-CH(CH_3)-CH_3$	H	–	–
44.)	O	H	H	$-CH_2-C(CH_3)_3$	H	–	–
45.)	O	H	H	$-CH_2CH_2CH_2CH_2CH_2CH_3$	H	–	–

Compound	X	R^1	R	R^6	R^8	R^7	Q
46.)	O	H	H	$-CH(CH_3)CH(CH_3)_2$ CH_3	H	–	–
47.)	O	H	H	$-CH_2CH=CH_2$	H	–	–
48.)	O	H	H	$-CH_2CH-CH_3$ CH_3	H	–	–
49.)	O	H	H	$-CH-CH=CH_2$ CH_2	H	–	–
50.)	O	H	H	$-CH_2CH=CH-CH_3$	H	–	–
51.)	O	H	H	$-CH_2-CH_2-CH=CH_2$ CH_3	H	–	–
52.)	O	H	H	$-CH-CH=CH_2$ C_2H_5	H	–	–
53.)	O	H	H	$-CH_2-CH=CH-CH_2CH_3$	H	–	–
54.)	O	H	H	$-CH_2CH=CH-CH_2CH_2CH_3$	H	–	–
55.)	O	H	H	$-CH_2-C=CH-CH_2CH_3$ CH_3	H	–	–

Compound	X	R^1	R	R^5	R^6	R^7	Q
56.)	O	H	H	$-CH_2-CH-CH=CH-CH_3$	H	–	–
57.)	O	H	H	$CH_3CH-CH=CH-CH_3$ $\vert$ CH_3	H	–	–
58.)	O	H	H		H	–	–
59.)	O	H	H		H	–	–
60.)	O	H	H		H	–	–
61.)	O	H	H		H	–	–
62.)	O	H	H		H	–	–

Compound	X	R^1	R	R^5	R^6	R^7	Q
63.)	O	H	H		H	–	–
64.)	O	H	H		H	–	–
65.)	O	H	H		H	–	–
66.)	O	H	H		H	–	–
67.)	O	H	H	$-CH_2-CH=CH-\phi$	H	–	–
68.)	O	H	H		H	–	–
69.)	O	H	H	$-CH_3$	$-CH_2CH=CH_2$ $\vert$ CH_3	–	–

Compound	X	R^3	R	R^5	R^6	R^7	Q
70.)	O	H	H	$-CH_3$	$-CH_2CH=CH-CH_3$	–	–
71.)	O	H	H	$-CH_3$	$-CH(CH_3)-CH=CH_2$	–	–
72.)	O	H	H	$-CH_3$	$-CH=CH-CH_2CH_3$	–	–
73.)	O	H	H	$-CH_3$	$-CH_2-C(CH_3)=CH_2-CH_3$	–	–
74.)	O	H	H	$-CH_3$	$-CH_2-CH=CH-CH(CH_3)-CH_3$	–	–
75.)	O	H	H	$-CH_3$		–	–
76.)	O	H	H	$-CH_3$		–	–
77.)	O	H	H	$-CH_3$		–	–

Compound	X	R^3	R	R^5	R^6	R^7	Q
78.)	O	H	H	$-CH_3$		–	–

Example 33.

Preparation of Pharmaceutical Compositions

One such unit dosage form consists in mixing 120 mg. of N,N,N - trimethyl - thienamycin chloride with 20 mg. of lactose and 5 mg. of magnesium stearate and placing the 145 mg. mixture into a No. 3 gelatin capsule. Similarly, by employing more of the active ingredient and less lactose, other dosage forms can be put up in No. 3 gelatin capsules and should it be necessary to mix more than 145 mg. of ingredients together, larger capsules such as compressed tablets and pills can also be prepared. The following examples are illustrative of the preparation of pharmaceutical formulations:

TABLET	PER TABLET
N,N,N - trimethyl - thienamycin chloride	125 mg.
Cornstarch, U.S.P.	6mg.
Dicalcium Phosphate	192 mg.
Lactose, U.S.P.	190 mg.

The active ingredient is blended with the di-calcium phosphate, lactose and about half of the cornstarch. The mixture is then granulated with 15% cornstarch paste (6 mg.) and rough-screened. It is dried at 45°C, and screened again through No. 16 screens. The balance of the cornstarch and the magnesium stearate is added and the mixture is compressed into tablets, approximately 0.5 inch in diameter each weighing 800 mg.

PARENTERAL SOLUTION

Ampoule:	PER TABLET
N,N,N - trimethyl - thienamycin chloride	500 mg.
Diluent: Sterile Water for Injection	2cc.

OPTHALMIC SOLUTION

N,N,N - trimethyl - thienamycin chloride	100 mg.
Hydroxypropylmethyl Cellulose	5 mg.
Sterile Water	to 1 ml.

OTIC SOLUTION

N,N,N - trimethyl - thienamycin chloride	100 mg.
Benzalkonium Chloride	0.1 mg.
Sterile Water	to 1 ml.

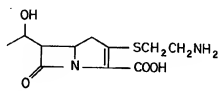
TOPICAL OINTMENT

N,N,N - trimethyl - thienamycin chloride	100 mg.
Polyethylene Glycol 4000 U.S.P.	400 mg.
Polyethylene Glycol 400 U.S.P.	1.0 gram

The active ingredient in the above formulations may be adminstered alone or in combination with other biologically active ingredients as, for example, with other antibacterial agents such as lincomycin, a penicillin, streptomycin, novobiocin, gentamicin, neomycin, colistin, and kanamycin, or with other therapeutic agents such as probenecid.

PREPARATION OF ALTERNATIVE STARTING MATERIALS

It will be recognized that, in addition to thienamycin itself its various stereoisomers, alone or as mixtures, may serve as starting materials in the preparation of the compounds of the present invention. Some of these isomers are obtainable from natural products of fermentation as described and claimed in the specifications of our copending applications Nos. 48233/76 (Serial No. 1561108) and 48235/76 (Serial No. 1561109). Attention is directed in particular to the preparation of Antibiotics 890A, and 890A$_2$ by the processes described in Examples 6 and 7 of the specification of application No. 48235/76 (Serial No. 1561109). These compounds can then be treated to cleave the N - acetyl group to provide the free base

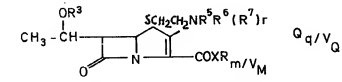


I

Moreover, by total synthesis all isomers can be made available as described in the specification of our copending application No. 48236/76 (Serial No. 1570986) as a mixture of four diastereoisomers which possess antibacterial activity and which are amenable to resolution by conventional techniques. The four diastereoisomers (two *cis*, two *trans*) are separable by chromatography. Resolution of any given *d/l* pair with optically active acids or bases proceeds according to conventional techniques.

WHAT WE CLAIM IS:—

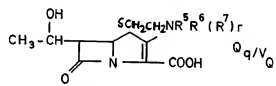
1. A compound having the general formula:



in which X is oxygen, sulfur, imino (—NH—) or —NR—, Q is an anion, R is a hydrogen atom, an alkali or alkaline-earth metal or amine cation, a univalent blocking group or a pharmaceutically acceptable ester or amide residue; R^3 is a hydrogen atom, an acyl radical or a residue such that OR^3 is classifiable to an ether group; each of R^5, R^6 and (if present) R^7, which are alike or different, is a hydrogen atom (provided that not all of R^5, R^6 and R^7 are hydrogen at the same time), or a substituted or unsubstituted C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl radical or an unsubstituted or ring-substituted C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $(C_{3-8}$ cycloalkenyl) - $(C_{1-6}$ alkyl), $(C_{3-8}$ cycloalkyl) - $(C_{1-6}$ alkyl), C_{6-10} aryl, $(C_{6-10}$ aryl) - $(C_{1-6}$ alkyl) or $(C_{6-10}$ aryl) - $(C_{2-6}$ alkenyl) radical or an unsubstituted or ring-substituted monocyclic or bicyclic heteroaryl or heteroaralkyl comprising 4—10 ring atoms, one or more of which is oxygen, nitrogen or sulphur, and 1—6 carbon atoms in the alkyl chain; and in which the substituent(s) is or are chlorine, bromine, iodine, fluorine, azido, cyano, amino, C_{1-6} alkylamino, di$(C_{1-6}$ alkyl)amino, a tri$(C_{1-6}$ alkyl)ammonium salt, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkylthioalkyl, carboxyl, oxo (through oxo cannot be present on the nitrogen-attached carbon), $(C_{1-6}$ alkoxy)carbonyl, C_{2-10} acyloxy, carbamoyl, $(C_{1-4}$ alkyl)carbamoyl, di$(C_{1-4}$ alkyl)-carbamoyl, cyanothio (—SCN) or nitro, or R_5 and R_6 are joined to form a polyethylene or oxygen-interrupted polymethylene residue;

V_Q and V_M are the valencies of Q and R respectively, V_M being 1 when R is other than a cation, and each of m, q, and r is 0 or 1 and such that $m + r - q = 1$.

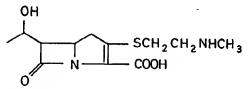
2. A compound having the general formula:



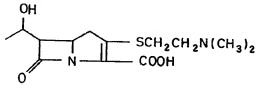
or a pharmaceutically acceptable salt, ether, amide or ester thereof, in which R^5, R^6, R^7, Q, q, r and V_Q are as defined in Claim 1.

3. A compound as claimed in Claim 2 in which each of R^5, R^6 and R^7 is hydrogen or C_{1-6} alkyl.

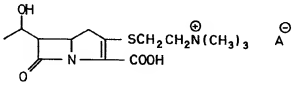
4. A compound having the formula:



5. A compound haing the formula:



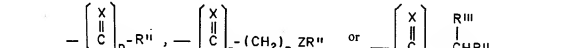
6. A compound having the formula:



where A^- is a univalent pharmaceutically acceptable anion.

7. A compound as claimed in Claim 1 in which R is hydrogen; C_{1-10} alkyl, phenacyl, nuclear-substituted phenacyl in which the substituent is chloro, bromo, fluoro, or C_{1-5} alkyl; (C_{1-10} alkoxy) - (C_{1-5} alkyl) in which the alkoxy residue is open-chain or cyclic; (C_{1-5} alkanoyloxy) - (C_{1-5} alkyl); halogenated C_{1-5} alkyl in which the halo is chlorine, bromine, iodine and/or fluorine; C_{2-10} alkenyl; C_{3-14} alkoxycarbonylalkyl; C_{4-21} dialkylaminoacetoxyalkyl; C_{2-19} alkanamidoalkyl; aralkyl in which the alkyl residue has 1 to 3 carbon atoms and the aryl residue 6 to 10 carbon atoms; monocyclic and bicyclic heteroaralkyl having 4 to 10 ring atoms and 1 to 6 carbon atoms in the alkyl residue, the hetero atom or atoms being oxygen, sulphur and/or nitrogen; nuclear-substituted aralkyl and heteroaralkyl in which the substituent is chlorine, fluorine, bromine, iodine, C_{1-5} alkyl, C_{1-5} alkanoyloxy or C_{1-5} alkoxy; mono- and bicyclic heterocyclylalkyl in which the heterocycle comprises 4 to 10 atoms and the hetero atom or atoms is oxygen, sulphur and/or nitrogen and the alkyl residue comprises 1 to 6 carbon atoms; aryl and nuclear-substituted aryl comprising 6 to 10 ring carbon atoms and in which the nuclear substituent is hydroxy, alkyl comprising 1 to 6 carbon atoms, chloro, fluoro or bromo; (C_{1-10} alkylthio) - (C_{1-5} alkyl), cycloalkylthioalkyl comprising 4 to 12 carbon atoms; acylathioalkyl in which the acyl residue comprises 2—10 carbon atoms and the alkyl residue comprises 1 to 6 carbon atoms.

8. A compound as claimed in Claim 7 in which R^3 is a radical of formula:

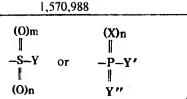


in which X is O or S; p is 0 or 1; n is 0, 1, 2, 3 or 4; Z is O, S,

R″ is hydrogen, amino, mercapto, hydroxy, substituted amino, substituted mercapto, substituted hydroxy, alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heteroaryl or heteroaralkyl, provided that R″ is not mercapto or hydroxy unless Z or R‴ is present, that R″ is not mercapto or hydroxy if Z is oxygen, that R″ is not amino or hydroxy if Z is sulfur and that R″ is not mercapto if Z is imino; and R‴ is azido, carbamoyl, guanidino, amidino, acyloxy, halo, sulfamino, sulfo, tetrazolyl, carboxy, alkoxycarbonyl, phosphono, alkoxy or arylthio.

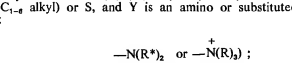
9. A compound as claimed as claimed in Claim 8 in which R″ is hydrogen, amino, C_{1-5} alkylamino, di(C_{1-5} alkyl)amino, C_{1-5} alkyl, C_{1-5} alkylthio, C_{6-10} arylthio, C_{1-5} alkoxy, C_{6-10} aryloxy, C_{2-5} alkenyl, C_{2-5} alkynyl, phenyl, benzyl, C_{3-5} cycloalkyl, or a monocyclic or bicyclic heteroaryl or heteroaryl(C_{1-3} alkyl) radical in which the heterocyclic ring(s) contain(s) from four to ten atoms, including at least one heteroatom from among oxygen, nitrogen and sulfur, the above mentioned hydrocarbon and heterocyclic radicals optionally having one or more hydroxy, mercapto, C_{1-5} alkylthio, arylthio, C_{1-5} alkoxy, C_{1-5} alkyl, halogen, cyano, carboxy, sulfamino, carbamoyl, sulfonyl, azido, amino, (C_{1-5} alkyl)-substituted amino, quaternary ammonium, C_{1-5} halogenated alkyl, carboxy-(C_{1-5} alkyl), carbamoyl-(C_{1-5} alkyl), N-substituted carbamoyl-(C_{1-5} alkyl), amidino, guanidino, N-substituted guanidino and/or guanidino-(C_{1-5} alkyl) substituents.

10. A compound according to Claim 1 in which R^2 is a radical of formula:

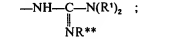


in which X is O or S; each of m and n, independently of the other, is 0 or 1; Y is $O^{\ominus}M^{\oplus}$, $-NR^*_2$ or R^*; where $M^{\oplus}$ is a hydrogen atom, an alkali metal or alkaline-earth metal cation, or an organic base; and R^* is hydrogen, amino, mercapto, hydroxy, alkylamino, dialkylamino, alkyl, alkylthio, arylthio, alkoxy, aralkoxy, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heteroaryl, or heteroaralkyl; and each of Y′ and Y″, independently of the other, is $O^{\ominus}M^{\oplus}$, $-NR^*_2$ or R^* where M and R^* are as defined above; or Y′ and Y″ are joined to form, together with the phosphorus atom to which they are attached, a cyclic ester or amide.

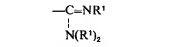
11. A compound according to Claim 1 in which R^3 is a radical of formula:



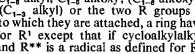
in which each of p and q, independently of the other, is 0 or 1; each of m and n, independently of the other, is 0, 1, 2, 3, 4, or 5; A is 0, $-NR^o-$ (where R^o is hydrogen or C_{1-6} alkyl) or S, and Y is an amino or substituted amino radical of formula:



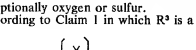
an amidino or substituted amidino radical of formula:



a guanidino or substituted guanidino radical of formula:



or a guanyl or substituted guanyl radical of formula:

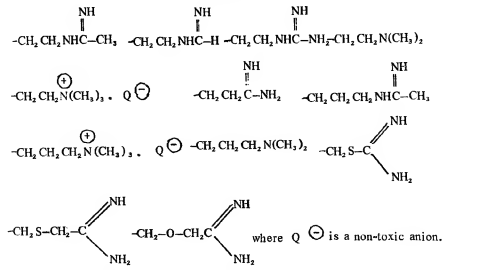


where each R^1, independently of the other, is hydrogen; $N(R^o)_2$ (where R^o is hydrogen or C_{1-6} alkyl); C_{1-6} alkyl, C_{1-6} alkoxy; (C_{1-6} alkoxy) - (C_{2-6} alkyl), C_{3-6} cycloalkyl or cycloalkyl-(C_{1-3} alkyl) or the two R groups are joined to form together with the N atom to which they are attached, a ring having 3 to 6 atoms; R^* is a radical as defined for R^1 except that if cycloalkylalkyl, it must be (C_{3-6} cycloalkyl) - C_{1-3} alkyl; and R^{**} is a radical as defined for R or a (C_{1-6} alkoxy)-methyl radical; or Y is a monocyclic or bicyclic heterocyclic aromatic or non-aromatic radical having 4 to 10 nuclear atoms and in which the hetero atom or atoms are nitrogen and optionally oxygen or sulfur.

12. A compound according to Claim 1 in which R^3 is a radical of formula:

in which p is 0 or 1 and R^{oo} is benzyl, p - hydroxybenzyl, 4 - amino - 4 - carboxybutyl, methyl, cyenomethyl, 2 - pentenyl, n - amyl, n - heptyl, ethyl, (3 or

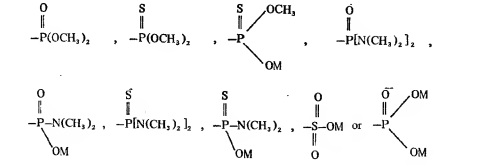
4) - nitrobenzyl, phenethyl, β,β - diphenylethyl, methyldiphenylmethyl, triphenylmethyl, 2 - methoxyphenyl, 2,6 - dimethoxyphenyl, 2,4,6 - trimethoxyphenyl, 3,5 - dimethyl - 4 - isoxazolyl, 3 - butyl - 5 - methyl - 4 - isoxazolyl, 5 - methyl - 3 - phenyl - 4 - isoxazolyl, 3 - (2 - chlorophenyl) - 5 - methyl - 4 - isoxazolyl, 3 - (2,6 - dichlorophenyl - 5 - methyl - 4 - isoxazolyl, *D* - 4 - amino - 4 - carboxybutyl, *D* - 4 - N - benzoylamino - 4 - carboxy - *n* - butyl, *p* - aminobenzyl, *o* - aminobenzyl, *m* - aminobenzyl, *p* - dimethylaminobenzyl, (3 - pryidyl)methyl, 2 - ethoxy - 1 - napthyl, 3 - carboxy - 2 - quinoxalinyl, 3 - (2,6 - dichlorophenyl) - 5 - (2 - furyl) - 4 - isoxazolyl, 3 - phenyl - 4 - isoxazolyl, 5-methyl - 3 - (4 - guanidinophenyl) - 4 - isoxazolyl, 4 - guanidinomethylphenyl, 4 - guanidinomethylbenzyl, 4 - guanidinobenzyl, 4 - guanidinophenyl, 2,6 - dimethoxy - 4 - guanidinophenyl, *o* - sulfobenzyl, *p* - carboxymethylbenzyl, *p* - carbamoylmethylbenzyl, *m* - fluorobenzyl, *m* - bromohenzyl, *p* - chlorobenzyl, *p* - methoxybenzyl, 1 - naphthylmethyl, 3 - isothiazolylmethyl, 4 - isothiazolylmethyl, 5 - isothiazolylmethyl, guanylthiomethyl, 4 - pyridylmethyl, 5 - isoxazolylmethyl, 4 - methoxy - 5 - isoxazolylmethyl, 4 - methyl - 5 - isoxazolylmethyl, 1 - imidazolylmethyl, 2 - benzofuranylmethyl, 2 - indolylmethyl, 2 - phenylvinyl, 2 - phenylethylnyl, 1 - aminocyclohexyl, 2- and 3 - thienylaminomethyl, 2 - (5 - nitrofuranyl)vinyl, phenyl, *o* - methoxyphenyl, *o* - chlorophenyl, *o* - phenylphenyl, *p* - aminomethylbenzyl, 1 - (5 - cyanotriazolyl)methyl, difluoromethyl, dichloromethyl, dibromomethyl, 1 - (3 - methylimidazolyl)methyl, (2 or 3) - (5 - carboxymethylthienyl)methyi, (2 or 3) - (4 - carbomoylthienyl)methyl, (2 or 3) - 5 - methylthienyl)methyl, (2 or 3) - (5 - methoxythienyl)methyl, (2 or 3) - (4 - chlorothienyl) - methyl, (2 or 3) - (5 - sulfothienyl)methyl, (2 or 3) - (5 - carboxythienyl)methyl, 3 - (1,2,5 - thiadiazolyl)methyl, 3 - (4 - methoxy - 1,2,5 - thiadiazolyl)methyl, 2 - furylmethyl, 2 - (5 - nitrofuryl)methyl, 3 - furylmethyl, 2 - thienylmethyl, 3 - thienylmethyl, tetrazolylmethyl, benzamidinomethyl, cyclohexylamidinomethyl, allylthiomethyl, phenylthiomethyl, butylthiomethyl, α - ctllorocrotylthiomethyl, phenoxymethyl, phenoxyethyl, phenoxybutyl, phenoxybenzyl, phenoxyphenoxymethyl, (dimethylmethoxy)methyl, (dimethylbutoxy)-methyl, (dimethylphenoxy)methyl, 4 - guanidinophenoxymethyl, 4 - pyridylthiomethyl, *p* - (carboxymethyl)phenoxymethyl, *p* - (carboxymethyl)phenylthiomethyl, 2 - thiazolylthiomethyl, *p* - (sulfo)phenoxymethyl, 2 - primidinylthiomethyl, phenethylthiomethyl, 1 - (5,6,7,8 - tetrahydronaphthyl)oxymethyl, N - methyl - 4 - pyridylthio, benzyloxy, methoxy, ethoxy, phenoxy, phenylthio, amino, methylamino, dimethylamino, a pyridinium methyl or trimethylammoniummethyl non-toxic salt, cyanomethylthiomethyl, trifluoromethylthiomethyl, 4 - pyridylethyl, 4 - pyridylpropyl, 4 - pyridylbutyl, 3 - imidazolyethyl, 3 - imidazolylpropyl, 3 - imidazolylbutyl, 1 - pyrrolylethyl, 1 - pyrrolylpropyl, 1 - pyrrolylbutyl, α - aminobenzyl, α - amino - (2 - thienyl)methyl, α - (methylamino) - benzyl, α - amino - methylthiopropyl, α - amino - 3 - or 4 - chlorobenzyl, α - amino - 3 or 4 - hydroxybenzyl, α - amino - 2,4 - dichlorobenzyl, α - amino - 3,4 - dichlorobenzyl, *D*(-) - α - hydroxybenzyl, α - carboxybenzyl, α - amino - (3 - thienyl)-methyl, *D*(-) - α - amino - 3 - chloro - 4 - hydroxybenzyl, α - amino(cyclohexyl)-methyl, α - (5 - tetrazolyl) - benzyl, 2 - thienyl - carboxymethyl, 3 - thienyl-carboxymethyl, 2 - furyl - carboxymethyl, 3 - furyl - carboxymethyl, α - sulfaminobenzyl, 3 - thienyl - sulfaminomethyl, α - (N - methylsulfamino) - benzyl, *D*(-) - 2 - thienyl - guanidinomethyl, *D*(-) - α - guanidinobenzyl, α - guanylureidobenzyl, α - hydroxybenzyl, α - azidobenzyl, α - fluorobenzyl, 4 - (5 - methoxy - 1,3 - oxadiazolyl) - aminomethyl, 4 - (5 - methoxy - 1,3 - oxadiazolyl) - hydroxymethyl, 4 - (5 - methoxy - 1,3 - sulfodiazolyl) - hydroxymethyl, 4 - (5 - chlorothienyl) - aminomethyl, 2 - (5 - chlorothienyl) - hydroxymethyl, 2 - (5 - chlorothienyl) - carboxymethyl, 3 - (1,2 - thiazolyl) - aminomethyl, 3 - (1,2 - thiazolyl) - hydroxymethyl, 3 - (1,2 - thiazolyl) - carboxymethyl, 2 - (1,4 - thiazolyl)aminomethyl, 2 - (1,4 - thiazolyl)hydroxymethyl, 2 - (1,4 - thiazolyl)carboxymethyl, 2 - benzothienylaminomethyl, 2 - benzothienyl-hydroxymethyl, 2 - benzothienylcarboxymethyl, α - sulfobenzyl, α - phosphonobenzyl, α - diethylphosphono, α - monoethylphosphono or a radical of formula:



13. A compound as claimed in Claim 12 in which X is oxygen and R is hydrogen, methyl, *t* - butyl, phenacyl, *p* - bromophenacyl, pivaloyloxymethyl, 2,2,2 - trichloroethyl, allyl, 3 - methyl - 2 - butenyl, 2 - methyl - 2 - propenyl, benzyl, benzhydryl, *p* - *t* - butylbenzyl, phthalidyl, phenyl, 5 - indanyl, acetylthiomethyl, acetoxymethyl, propionyloxymethyl, methallyl, 3 - butenyl, 4 - pentenyl, 2 - butenyl, acetoxyacetylmethyl pivaloyloxyacetylmethyl, diethylaminoethyl, dimethylaminoethyl, methoxymethyl, *p* - acetoxybenzyl, *p* - pivaloyloxybenzyl, *p* - isopropoxybenzyl, 5 - indanylmethyl, benzyloxymethyl, methylthioethyl, dimethylaminoacetoxymethyl, crotonolacton - 3 - yl, acetamidomethyl, acetylthioethyl, pivaloylthiomethyl or methylthiomethyl.

14. A compound as claimed in Claim 1 in which R^2 is formyl, propionyl, butyryl, chloroacetyl, methoxyacetyl, aminoacetyl, methoxycarbonyl, ethoxycarbonyl, methylcarbamoyl, ethylcarbamoyl, phenylthiocarbonyl, 3 - aminopropionyl, 4 - aminobutyryl, N - methylaminoacetyl, N,N - dimethylaminoacetyl, an N,N,N - trimethylaminoacetyl non-toxic salt, 3 - (N,N - dimethyl)aminopropionyl, an 3 - (N,N,N - trimethyl)amino propionyl, N,N,N - triethylaminoacetyl, or pyridiniumacetyl non-toxic salt, guanylthioacetyl, guanidinoacetyl, 3 - guanidinopropionyl, N^3 - methylguanidinopropionyl, hydroxyacetyl, 3 - hydroxypropionyl, acryloyl, propynoyl, malonyl, phenoxycarbonyl, amidinoacetyl, acetamidinoacetyl, amidinopropionyl, acetamidinopropionyl, guanylureidoacetyl, guanylcarbamoyl, carboxymethylaminoacetyl, sulfoacetylaminoacetyl, phosphonoacetylaminoacetyl, N^3 - dimethylaminoacetamidinopropionyl, ureidocarbonyl, dimethylaminoguanylthioacetyl, a 3 - (1 - methyl - 4 - pyridiniumpropionyl non-toxic salt, 3 - (5 - aminoimidazol - 1 - yl)-propionyl, a 3 - methyl - 1 - imidazoliumacetyl non-toxic salt, 3 - sydnonylacetyl, *o* - aminomethylbenzoyl or *o* - aminobenzoyl.

15. A compound as claimed in Claim 1 in which R^3 is



where M is hydrogen or an alkali metal or alkaline-earth metal cation.

16. A compound as claimed Claim 13 in which R^3 is sulfo, phosphono, carbamoyl, methylsulfonyl, sulfamoyl, dimethylsulfamoyl, N - methylcarbamoyl, bromoacetyl, hydroxyacetyl, aminoacetyl, dimethylaminoacetyl, trimethylammoniumacetyl, amidinoacetyl, guanidinoacetyl, methoxyacetyl, guanylacetyl, guanylthioacetyl, phosphamoyl, phosphonothioyl, thiocarbamoyl, methoxymethyl, hydroxyethyl, methoxyethyl, dimethylaminomethyl, dimethylaminoethyl, methylthiomethyl, amidinomethyl, or guanidinoethyl.

17. A compound as claimed in Claim 1 in which X is oxygen;

R^3 is hydrogen, CH_3, SO_3H, CH_2OCH_3, $\overset{O}{\overset{\|}{C}}OCH_3$ or $\overset{O}{\overset{\|}{C}}CH_2NH_2$;

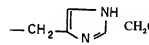
R is hydrogen, $CH_2\overset{O}{\overset{\|}{O}}CCH_3$, $CH_2OCH_2C(CH_3)_3$, $CH_2CH=CH_2$,

$CH_2\overset{CH_3}{\overset{|}{C}}=CH_2$, $CH_2CH_2N(C_2H_5)_2$, *p*-nitrobenzyl, $CH_2CH_2CH_3$, $CH_2CH_2CH_3$, $CH_2CH_2N(CH_3)_2$ benzoylmethyl, CH_2SCH_3, or

$CH_2\overset{O}{\overset{\|}{O}}C(CH_3)_3$; and each of R^5, R^6 and (if present) R^7, is, independently of the others, hydrogen (except that not all of R^5, R^6, and R^7 are hydrogen at the same time),

CH_3, CH_2CH_3, $CH_2CH=CH_2$, $CH_2CH_2CH_3$, $CH_2(C_6H_5)$, $CH(C_6H_5)_2$, $C(C_6H_5)_3$,

$CH_2\overset{CH_3}{\overset{|}{C}}=CH_2$, CH_2OCH_3, $CH_2CH=CH-CH_3$ $CH_2CH_2CH=CH_2$,



$CH_2CH_2\overset{+}{N}(CH_3)_3$, $CH_2\overset{O}{\overset{\|}{C}}CH_3$, $CH_2CH_2(OCH_3)_2$,

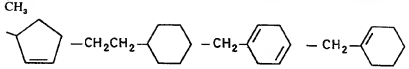
$CH_2-C\equiv CH$, $-CH_2CH_2OCH_2CH_2-$, $CH_2\overset{O}{\overset{\|}{C}}(C_6H_5)$, CH_2SCH_3,

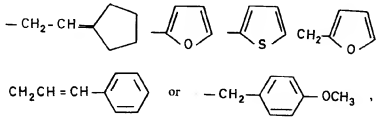
$CH_2O\overset{O}{\overset{\|}{C}}(CH_3)_3$, $CH_2CH_2C\equiv N$, $CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$,

$CH_2\overset{CH_3}{\overset{|}{C}}HCH_3$, $CH\overset{CH_3}{\overset{|}{C}}HCH_3$, $CH\overset{CH_3}{\overset{|}{C}}HCH_2CH_3$, $CH_2CH_2CH_2CH_2CH_3$,

$CH_2\overset{CH_3}{\overset{|}{C}}HCH_2CH_3$, $CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_3$, $CH(CH_3)-CH(CH_3)-CH_3$, $CH_2C(CH_3)_3$,

$CH\overset{CH_3}{\overset{|}{C}}HCH(CH_3)_2$, cyclopropyl, cyclopropylmethyl, 2,4 - dinitrophenyl,

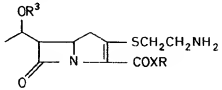




R_5 and R_6 together are trimethylene.

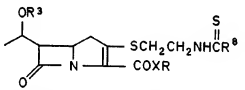
18. A compound as claimed in Claim 17 in which R^4 is hydrogen, X is oxygen, and R is hydrogen, or a pharmaceutically acceptable salt thereof.

19. A method of preparing a compound as claimed in Claim 1 comprising treating a compound of the formula:



in which R, R^3 and X are as defined in Claim 1, or an N - alkylated derivative thereof, with an alkylating agent calculated to provide the substituents R^5, R^6 and R^7.

20. A method of preparing a compound as claimed in Claim 1 comprising treating a compound of the formula:



in which R, R^3 and X are as defined in Claim 1 and R^8 is hydrogen, alkyl having from 1 to 5 carbon atoms or aralkyl having 6 to 10 ring carbon atoms and 1—5 carbon atoms in the alkyl chain, with a hydrogenation catalyst.

21. A method as claimed in Claim 19 in which the starting material is thienamycin or a suitably protected derivative.

22. A method of preparing a compound as claimed in Claim 1, substantially as hereinbefore described in any one of Examples 1, 2, 3, 5, 6, 8 to 13, 16 to 23, 25 to 28 and 31.

23. A compound as claimed in Claim 1 when prepared by a method as claimed in Claim 20, 21 or 22.

24. Each and every compound as claimed in Claim 1 hereinbefore individually specified.

25. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutical carrier.

26. A pharmaceutical composition comprising a compound according to Claim 2 and a pharmaceutical carrier.

27. A pharmaceutical composition comprising, in unitary dosage form, a therapeutically effective amount of a compound according to Claim 1 and a pharmaceutical carrier.

28. A pharmaceutical composition comprising, in unitary dosage form, a therapeutically effective amount of a compound according to Claim 2 and a pharmaceutical carrier.

29. A pharmaceutical composition as claimed in Claim 25 or 26, in the form of a capsule, tablet, powder, elixir, aqueous or oily solution or suspenstion, emulsion or syrup.

30. A composition as claimed in Claim 27 or 28, in orally administrable form.

31. A composition as claimed in Claim 25 or 26, in intravenously administrable form.

32. A composition as claimed in Claim 25 or 26, in intramuscularly administrable form.

33. A composition as claimed in Claim 25 or 26, in the form of a suppository.

34. A composition as claimed in Claim 25 or 26 in form suitable for absorption through the mucous membranes of the nose and throat or bronchial tissues.

35. A composition as claimed in Claim 25 or 26, in the form of a liquid spray or inhalant, a lozenge or a throat paint.

36. A composition as claimed in Claim 25 or 26, in aurally or optically administrable form.

37. A composition as claimed in Claim 25 or 26, in topically administrable form.

38. A composition as claimed in Claim 37, in the form of an ointment, cream, lotion, paint or powder.

39. An antibacterial composition comprising as active ingredient a compound as claimed in Claim 1 or 2 together with a material in respect of which antibacterial action is desired.

40. A composition as claimed in Claim 39 in which the said material is a human or animal foodstuff.

41. A composition as claimed in Claim 39 in which the said material is a water-based paint.

42. A composition as claimed in Claim 39 in which the said material is the white water of a paper mill.

43. A disinfectant comprising as active ingredient a compound as claimed in Claim 1 or 2 together with a carrier.

44. A veterinary composition comprising as active ingredient a compound as claimed in Claim 1 or 2 together with a non-toxic base material.

45. A composition as claimed in Claim 44 in the form of an intramammary preparation.

46. A composition as claimed in Claim 25, substantially as hereinbefore described with respect to any of the formulations set forth in Example 33.

47. A composition as claimed in any one of Claims 25 to 45 in which the said compound is a compound as claimed in any one of Claims 3 to 18.

48. A composition as claimed in any one of Claims 25 to 45 in which the said compound is a compound as claimed in Claim 23 or 24.

For the Applicants
D. YOUNG & CO.
Chartered Patent Agents
9 & 10 Staple Inn
London WC1V 7RD

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1980.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.